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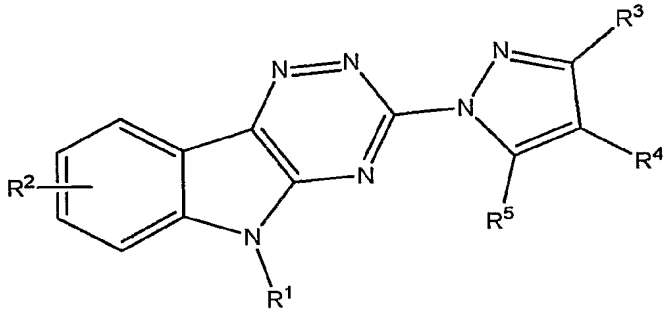


(I)

(57) Abstract: A compound of formula (I) wherein R^1 is hydrogen, alkyl, -alkyl-aryl, -alkyl-heterocycloalkyl or -alkyl-0-heterocycloalkyl; R^2 is hydrogen, hydroxy, amino, nitro, alkoxy, alkyl, aryl or heteroaryl; R^3 is hydrogen, alkyl or aryl; R^4 is hydrogen, alkyl, aryl, heteroaryl, -$CH(aryl)_2$, -alkyl-aryl or -C(0)0-alkyl; and R^5 is alkyl, hydroxy or amino; or a pharmaceutically acceptable salt thereof; is new for use in therapy, e.g. in the treatment of Alzheimer's disease.

WO 2004/096808 A1

TRIAZINE COMPOUNDS AND THEIR USE

Field of the Invention

This invention relates to compounds and their therapeutic use.

Background to the Invention

Alzheimer's disease (AD) is the most common form of dementia among older people, and affects parts of the brain that control thought, memory and language. Susceptibility to Alzheimer's disease increases with age, but the disease is not a normal part of the ageing process.

Alzheimer's disease is associated with regions of accumulated proteins in the brain. These dense regions, termed "amyloid plaques" and "neurofibrilliary tangles", contain β-amyloid precursor protein (β-APP). β-APP is degraded by β-amyloid converting enzyme (BACE, also known as β-secretase) to produce β-amyloid peptide Aβ 40/42, which accumulates in the plaques. Research has shown that the activity of BACE is an early step in the pathogenesis pathway common to all familial and sporadic forms of AD; thus inhibitors of BACE may have therapeutic utility in the treatment of this disease.

The following compounds are known:

2-(3,5-dimethyl-pyrazol-1-yl)-9-ethyl-9H-1,3,4,9-tetraaza-fluorene;

2-(3,5-dimethyl-pyrazol-1-yl)-9-methyl-9H-1,3,4,9-tetraaza-fluorene;

9-benzyl-2-(3,5-dimethyl-pyrazol-1-yl)-9H-1,3,4,9-tetraaza-fluorene;

9-benzyl-2-(4-benzyl-3,5-dimethyl-pyrazol-1-yl)-9H-1,3,4,9-tetraaza-fluorene;

4-benzyl-2-(9-benzyl-9H-1,3,4,9-tetraaza-fluoren-2-yl)-5-methyl-2H-pyrazol-3-ol;

2-(4-butyl-3,5-dimethyl-pyrazol-1-yl)-9-ethyl-9H-1,3,4,9-tetraaza-fluorene;

2-(4-benzyl-3,5-dimethyl-pyrazol-1-yl)-9-ethyl-9H-1,3,4,9-tetraaza-fluorene;

3-(3,5-dimethyl-pyrazol-1-yl)-5*H*-1,2,4-triazino[5,6-*b*]indole;

5-methyl-2-(5*H*-1,2,4-triazino[5,6-*b*]indol-3-yl)-2*H*-pyrazol-3-ol;

5-(4-chloro-phenyl)-2-(5*H*-1,2,4-triazino[5,6-*b*]indol-3-yl)-2*H*-pyrazol-3-ol;

3-(3,5-dimethyl-pyrazol-1-yl)-8-fluoro-5*H*-1,2,4-triazino[5,6-*b*]indole;

5-amino-1-(5-ethyl-5*H*-1,2,4-triazino[5,6-*b*]indol-3-yl)-1*H*-pyrazole-4-carboxylic acid ethyl ester;

5-amino-1-(5*H*-1,2,4-triazino[5,6-*b*]indol-3-yl)-1*H*-pyrazole-4-carboxylic acid ethyl ester;

5-phenyl-2-(5*H*-1,2,4-triazino[5,6-*b*]indol-3-yl)-2*H*-pyrazol-3-ylamine;

2-(5-methyl-5*H*-1,2,4-triazino[5,6-*b*]indol-3-yl)-5-phenyl-2*H*-pyrazol-3-ylamine;

5-(4-chloro-phenyl)-2-(5-methyl-5*H*-1,2,4-triazino[5,6-*b*]indol-3-yl)-2*H*-pyrazol-3-ylamine;

5-(4-bromo-phenyl)-2-(5-methyl-5*H*-1,2,4-triazino[5,6-*b*]indol-3-yl)-2*H*-pyrazol-3-ylamine;

5-(4-bromo-phenyl)-2-(5*H*-1,2,4-triazino[5,6-*b*]indol-3-yl)-2*H*-pyrazol-3-ylamine;

5-(4-chloro-phenyl)-2-(5*H*-1,2,4-triazino[5,6-*b*]indol-3-yl)-2*H*-pyrazol-3-ylamine;

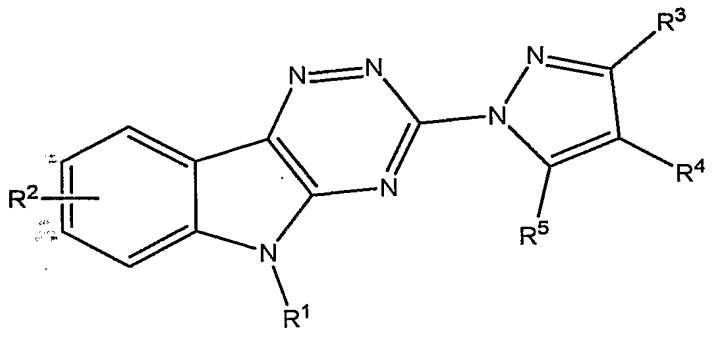
2-(8-bromo-5*H*-1,2,4-triazino[5,6-*b*]indol-3-yl)-5-phenyl-2*H*-pyrazol-3-ylamine;

2-(8-bromo-5*H*-1,2,4-triazino[5,6-*b*]indol-3-yl)-5-(4-chloro-phenyl)-2*H*-pyrazol-3-ylamine; and

5-(4-bromo-phenyl)-2-(8-bromo-5*H*-1,2,4-triazino[5,6-*b*]indol-3-yl)-2*H*-pyrazol-3-ylamine.

Summary of the Invention

A first aspect of the invention is a compound of formula (I)



(I)

wherein

R^1 is hydrogen, alkyl, -alkyl-aryl, -alkyl-heterocycloalkyl or -alkyl-O-heterocycloalkyl;

R^2 is hydrogen, hydroxy, amino, nitro, alkoxy, alkyl, aryl or heteroaryl;

R^3 is hydrogen, alkyl or aryl;

R^4 is hydrogen, alkyl, aryl, heteroaryl, $-CH(aryl)_2$, -alkyl-aryl or -C(O)O-alkyl; and

R^5 is alkyl, hydroxy or amino;

or a pharmaceutically acceptable salt thereof.

These compounds are new, for use in therapy. With the exception of the compounds identified in the Background section of the present specification, they are new *per se*.

Compounds of the invention may act as inhibitors of BACE and as a consequence may have utility in the treatment or prevention of diseases or conditions in which BACE is implicated. In particular, they may have utility in the treatment or prevention of a disease or condition associated with the deposition and/or elevated levels of amyloid beta peptide (Aβ), for example Alzheimer's disease.

Another aspect of the invention is a pharmaceutical composition comprising a compound of formula (I) and a pharmaceutically acceptable carrier or diluent.

Description of the Invention

For the present invention, certain compounds and combinations of substituents are preferred; in particular, see the sub-claims.

With regard to formula (I), R^1 is preferably hydrogen, methyl, ethyl, propyl, isopropyl, butyl, pyrazol-1-ylethyl, hydroxyethyl, (2-tetrahydro-pyran-2-yloxy)ethyl or benzyl. R^2 is preferably hydrogen. R^3 is preferably hydrogen, methyl or phenyl. Preferably R^4 is hydrogen, methyl, ethyl, propyl, butyl or $-C(O)OCH_2CH_3$. Other preferences for R^4 include phenyl, $-CH(phenyl)_2$, benzyl, 1-phenylethyl, 2-phenylethyl, naphthylmethyl, quinolin-4-yl and pyridin-2-yl, any of which is optionally substituted. R^5 is preferably hydrogen, methyl, hydroxy or amino.

The term "alkyl" as used herein refers to an optionally substituted straight or branched chain alkyl moiety having from one to six carbon atoms. The term includes, for example, methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, pentyl, hexyl and the like. The group may be substituted with one or more substituents selected from hydroxy, amino, halogen and the like. "C_{1-6} alkyl" has the same meaning.

The term "alkoxy" as used herein refers to a straight or branched chain alkoxy group containing one to six carbon atoms. The term includes, for example, methoxy, ethoxy, propoxy, isopropoxy, butoxy, tert-butoxy, pentoxy, hexoxy and the like. "C_{1-6} alkoxy" has the same meaning.

The term "halogen" as used herein refers to F, Cl, Br or I.

The term "heterocycloalkyl" as used herein refers to a saturated heterocyclic moiety having from three to seven ring carbon atoms and one or more ring heteroatoms selected from nitrogen, oxygen and sulphur. The term includes, for example, azetidinyl, pyrrolidinyl, tetrahydrofuranyl, piperidinyl and the like.

The term "aryl" as used herein refers to an optionally substituted aromatic ring system having six to fourteen ring carbon atoms. The group may be a polycyclic ring system, having two or more rings, at least one of which is aromatic. This term includes, for example, phenyl and naphthyl. The group may be substituted with one or more substituents selected from alkoxy, alkylamino, dialkylamino, halogen, hydroxy, nitro, benzyloxy, -OC(O)C(O)O-alkyl, $-CF_3$, $-S(O)_2$-alkyl, -OC(O)-alkyl, alkyl, -C(O)O-alkyl and -C(O)OH and the like.

The term "heteroaryl" as used herein refers to an optionally substituted aromatic ring system having from four to fourteen ring carbon atoms and, in addition, at least one ring heteroatom selected from nitrogen, oxygen and sulphur. The group may be a polycyclic ring system, having two or more rings, at least one of which is aromatic. The term includes, for example, furanyl, thiophenyl, pyridyl, indolyl, quinolyl and the like. The group may be substituted with, for example, one or more of the substituents named in the definition of "aryl".

Preferred compounds of the invention include:

2-(3,5-dimethyl-pyrazol-1-yl)-9-ethyl-9H-1,3,4,9-tetraaza-fluorene;

2-(3,5-dimethyl-pyrazol-1-yl)-9-methyl-9H-1,3,4,9-tetraaza-fluorene;

9-benzyl-2-(3,5-dimethyl-pyrazol-1-yl)-9H-1,3,4,9-tetraaza-fluorene;

9-benzyl-2-(4-benzyl-3,5-dimethyl-pyrazol-1-yl)-9H-1,3,4,9-tetraaza-fluorene;

4-benzyl-2-(9-benzyl-9H-1,3,4,9-tetraaza-fluoren-2-yl)-5-methyl-2H-pyrazol-3-ol;

2-(4-butyl-3,5-dimethyl-pyrazol-1-yl)-9-ethyl-9H-1,3,4,9-tetraaza-fluorene;

2-(4-benzyl-3,5-dimethyl-pyrazol-1-yl)-9-ethyl-9H-1,3,4,9-tetraaza-fluorene;

9-methyl-2-(5-methyl-3-phenyl-pyrazol-1-yl)-9H-1,3,4,9-tetraaza-fluorene;

2-(3,5-dimethyl-4-propyl-pyrazol-1-yl)-9-methyl-9H-1,3,4,9-tetraaza-fluorene;

5-amino-1-(9-methyl-9H-1,3,4,9-tetraaza-fluoren-2-yl)-1H-pyrazole-4-carboxylic acid ethyl ester;

3-(4-ethyl-3,5-dimethyl-pyrazol-1-yl)-5H-1,2,4-triazino[5,6-b]indole;

3-(4-benzyl-3,5-dimethyl-pyrazol-1-yl)-5H-1,2,4-triazino[5,6-b]indole;

3-[4-(2-benzyloxy-benzyl)-3,5-dimethyl-pyrazol-1-yl]-5H-1,2,4-triazino[5,6-b]indole;

4-[3,5-dimethyl-1-(5H-1,2,4-triazino[5,6-b]indol-3-yl)-1H-pyrazol-4-ylmethyl]-phenol;

2-[3,5-dimethyl-1-(5H-1,2,4-triazino[5,6-b]indol-3-yl)-1H-pyrazol-4-ylmethyl]-phenol;

3-[3,5-dimethyl-1-(5H-1,2,4-triazino[5,6-b]indol-3-yl)-1H-pyrazol-4-ylmethyl]-phenol;

3-[4-(3,5-dimethoxy-benzyl)-3,5-dimethyl-pyrazol-1-yl]-5H-1,2,4-triazino[5,6-b]indole;

3-(3,5-dimethyl-4-naphthalen-2-ylmethyl-pyrazol-1-yl)-5H-1,2,4-triazino[5,6-b]indole;

3-[4-(2-fluoro-benzyl)-3,5-dimethyl-pyrazol-1-yl]-5H-1,2,4-triazino[5,6-b]indole;

3-[3,5-dimethyl-4-(3-trifluoromethyl-benzyl)-pyrazol-1-yl]-5H-1,2,4-

triazino[5,6-b]indole;

3-[4-(2-methoxy-benzyl)-3,5-dimethyl-pyrazol-1-yl]-5-methyl-5H-1,2,4-triazino[5,6-b]indole;

3-[4-(3-fluoro-benzyl)-3,5-dimethyl-pyrazol-1-yl]-5-methyl-5H-1,2,4-triazino[5,6-b]indole;

3-[4-(3-methoxy-benzyl)-3,5-dimethyl-pyrazol-1-yl]-5-methyl-5H-1,2,4-triazino[5,6-b]indole;

3-[4-(3,5-dimethoxy-benzyl)-3,5-dimethyl-pyrazol-1-yl]-5-methyl-5H-1,2,4-triazino[5,6-b]indole;

3-[3,5-dimethyl-4-(2-nitro-benzyl)-pyrazol-1-yl]-5-methyl-5H-1,2,4-triazino[5,6-b]indole;

3-[4-(2-fluoro-benzyl)-3,5-dimethyl-pyrazol-1-yl]-5-methyl-5H-1,2,4-triazino[5,6-b]indole;

2-[3,5-dimethyl-1-(5-methyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)-1H-pyrazol-4-ylmethyl]-phenol;

3-[4-(4-methoxy-benzyl)-3,5-dimethyl-pyrazol-1-yl]-5-methyl-5H-1,2,4-triazino[5,6-b]indole;

3-[4-(2-benzyloxy-benzyl)-3,5-dimethyl-pyrazol-1-yl]-5-methyl-5H-1,2,4-triazino[5,6-b]indole;

3-(3,5-dimethyl-4-naphthalen-2-ylmethyl-pyrazol-1-yl)-5-methyl-5H-1,2,4-triazino[5,6-b]indole;

3-[3,5-dimethyl-4-(4-nitro-benzyl)-pyrazol-1-yl]-5-methyl-5H-1,2,4-triazino[5,6-b]indole;

4-[3,5-dimethyl-1-(5-methyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)-1H-pyrazol-4-ylmethyl]-phenol;

3-[3,5-dimethyl-1-(5-methyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)-1H-pyrazol-4-ylmethyl]-phenol;

3-[3,5-dimethyl-4-(4-trifluoromethyl-benzyl)-pyrazol-1-yl]-5-methyl-5H-1,2,4-triazino[5,6-b]indole;

3-[4-(4-methanesulphonyl-benzyl)-3,5-dimethyl-pyrazol-1-yl]-5-methyl-5H-1,2,4-triazino[5,6-b]indole;

3-[3,5-dimethyl-4-(2-trifluoromethyl-benzyl)-pyrazol-1-yl]-5-methyl-5H-

1,2,4-triazino[5,6-b]indole;

3-[3,5-dimethyl-4-(3-trifluoromethyl-benzyl)-pyrazol-1-yl]-5-methyl-5H-1,2,4-triazino[5,6-b]indole;

3-[3,5-dimethyl-4-(2-methyl-benzyl)-pyrazol-1-yl]-5-methyl-5H-1,2,4-triazino[5,6-b]indole;

3-[3,5-dimethyl-4-(3-methyl-benzyl)-pyrazol-1-yl]-5-methyl-5H-1,2,4-triazino[5,6-b]indole;

3-(3,5-dimethyl-4-phenethyl-pyrazol-1-yl)-5-methyl-5H-1,2,4-triazino[5,6-b]indole;

4-[3,5-dimethyl-1-(5-methyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)-1H-pyrazol-4-ylmethyl]-benzoic acid methyl ester;

3-[3,5-dimethyl-1-(5-methyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)-1H-pyrazol-4-ylmethyl]-benzoic acid methyl ester;

acetic acid 4-[3,5-dimethyl-1-(5-methyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)-1H-pyrazol-4-ylmethyl]-phenyl ester;

acetic acid 3-[3,5-dimethyl-1-(5-methyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)-1H-pyrazol-4-ylmethyl]-phenyl ester;

acetic acid 2-[3,5-dimethyl-1-(5-methyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)-1H-pyrazol-4-ylmethyl]-phenyl ester;

5-ethyl-3-[4-(2-methoxy-benzyl)-3,5-dimethyl-pyrazol-1-yl]-5H-1,2,4-triazino[5,6-b]indole;

5-ethyl-3-[4-(2-fluoro-benzyl)-3,5-dimethyl-pyrazol-1-yl]-5H-1,2,4-triazino[5,6-b]indole;

5-ethyl-3-[4-(3-fluoro-benzyl)-3,5-dimethyl-pyrazol-1-yl]-5H-1,2,4-triazino[5,6-b]indole;

5-ethyl-3-[4-(4-fluoro-benzyl)-3,5-dimethyl-pyrazol-1-yl]-5H-1,2,4-triazino[5,6-b]indole;

5-ethyl-3-[4-(3-methoxy-benzyl)-3,5-dimethyl-pyrazol-1-yl]-5H-1,2,4-triazino[5,6-b]indole;

3-[4-(3,5-dimethoxy-benzyl)-3,5-dimethyl-pyrazol-1-yl]-5-ethyl-5H-1,2,4-triazino[5,6-b]indole;

3-[3,5-dimethyl-4-(2-nitro-benzyl)-pyrazol-1-yl]-5-ethyl-5H-1,2,4-

triazino[5,6-b]indole;

2-[1-(5-ethyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)-3,5-dimethyl-1H-pyrazol-4-ylmethyl]-phenol;

5-ethyl-3-[4-(4-methoxy-benzyl)-3,5-dimethyl-pyrazol-1-yl]-5H-1,2,4-triazino[5,6-b]indole;

3-[4-(2-benzyloxy-benzyl)-3,5-dimethyl-pyrazol-1-yl]-5-ethyl-5H-1,2,4-triazino[5,6-b]indole;

3-(3,5-dimethyl-4-naphthalen-2-ylmethyl-pyrazol-1-yl)-5-ethyl-5H-1,2,4-triazino[5,6-b]indole;

3-[3,5-dimethyl-4-(3-nitro-benzyl)-pyrazol-1-yl]-5-ethyl-5H-1,2,4-triazino[5,6-b]indole;

3-[3,5-dimethyl-4-(4-nitro-benzyl)-pyrazol-1-yl]-5-ethyl-5H-1,2,4-triazino[5,6-b]indole;

4-[1-(5-ethyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)-3,5-dimethyl-1H-pyrazol-4-ylmethyl]-phenol;

3-[1-(5-ethyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)-3,5-dimethyl-1H-pyrazol-4-ylmethyl]-phenol;

3-[3,5-dimethyl-4-(4-trifluoromethyl-benzyl)-pyrazol-1-yl]-5-ethyl-5H-1,2,4-triazino[5,6-b]indole;

5-ethyl-3-[4-(4-methanesulphonyl-benzyl)-3,5-dimethyl-pyrazol-1-yl]-5H-1,2,4-triazino[5,6-b]indole;

3-[3,5-dimethyl-4-(2-trifluoromethyl-benzyl)-pyrazol-1-yl]-5-ethyl-5H-1,2,4-triazino[5,6-b]indole;

3-[3,5-dimethyl-4-(3-trifluoromethyl-benzyl)-pyrazol-1-yl]-5-ethyl-5H-1,2,4-triazino[5,6-b]indole;

3-[3,5-dimethyl-4-(2-methyl-benzyl)-pyrazol-1-yl]-5-ethyl-5H-1,2,4-triazino[5,6-b]indole;

3-[3,5-dimethyl-4-(3-methyl-benzyl)-pyrazol-1-yl]-5-ethyl-5H-1,2,4-triazino[5,6-b]indole;

3-(3,5-dimethyl-4-phenethyl-pyrazol-1-yl)-5-ethyl-5H-1,2,4-triazino[5,6-b]indole;

4-[1-(5-ethyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)-3,5-dimethyl-1H-pyrazol-4-

ylmethyl]-benzoic acid methyl ester;

3-[1-(5-ethyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)-3,5-dimethyl-1H-pyrazol-4-ylmethyl]-benzoic acid methyl ester;

4-[1-(5-ethyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)-3,5-dimethyl-1H-pyrazol-4-ylmethyl]-benzoic acid;

3-(3,5-dimethyl-4-propyl-pyrazol-1-yl)-5-ethyl-5H-1,2,4-triazino[5,6-b]indole;

5-ethyl-3-(4-ethyl-3,5-dimethyl-pyrazol-1-yl)-5H-1,2,4-triazino[5,6-b]indole;

3-(4-benzyl-3,5-dimethyl-pyrazol-1-yl)-5-propyl-5H-1,2,4-triazino[5,6-b]indole;

5-propyl-3-(3,4,5-trimethyl-pyrazol-1-yl)-5H-1,2,4-triazino[5,6-b]indole;

3-(4-ethyl-3,5-dimethyl-pyrazol-1-yl)-5-propyl-5H-1,2,4-triazino[5,6-b]indole;

3-(3,5-dimethyl-4-propyl-pyrazol-1-yl)-5-propyl-5H-1,2,4-triazino[5,6-b]indole;

5-butyl-3-(3,5-dimethyl-pyrazol-1-yl)-5H-1,2,4-triazino[5,6-b]indole;

5-butyl-3-(3,4,5-trimethyl-pyrazol-1-yl)-5H-1,2,4-triazino[5,6-b]indole;

3-(4-benzyl-3,5-dimethyl-pyrazol-1-yl)-5-butyl-5H-1,2,4-triazino[5,6-b]indole;

5-butyl-3-(3,5-dimethyl-4-naphthalen-2-ylmethyl-pyrazol-1-yl)-5H-1,2,4-triazino[5,6-b]indole;

5-butyl-3-[4-(2-fluoro-benzyl)-3,5-dimethyl-pyrazol-1-yl]-5H-1,2,4-triazino[5,6-b]indole;

5-butyl-3-[3,5-dimethyl-4-(3-trifluoromethyl-benzyl)-pyrazol-1-yl]-5H-1,2,4-triazino[5,6-b]indole;

5-butyl-3-(4-ethyl-3,5-dimethyl-pyrazol-1-yl)-5H-1,2,4-triazino[5,6-b]indole;

5-benzyl-3-(3,4,5-trimethyl-pyrazol-1-yl)-5H-1,2,4-triazino[5,6-b]indole;

3-(4-benzyl-3,5-dimethyl-pyrazol-1-yl)-5-isobutyl-5H-1,2,4-triazino[5,6-b]indole;

5-benzyl-3-(3,5-dimethyl-4-propyl-pyrazol-1-yl)-5H-1,2,4-triazino[5,6-b]indole;

oxalic acid 4-[3,5-dimethyl-1-(5-methyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)-

1H-pyrazol-4-ylmethyl]-phenyl ester ethyl ester;

5-isobutyl-3-(3,4,5-trimethyl-pyrazol-1-yl)-5H-1,2,4-triazino[5,6-b]indole;

3-(4-ethyl-3,5-dimethyl-pyrazol-1-yl)-5-isobutyl-5H-1,2,4-triazino[5,6-b]indole;

3-(3,5-dimethyl-4-propyl-pyrazol-1-yl)-5-isobutyl-5H-1,2,4-triazino[5,6-b]indole;

3-(3,5-dimethyl-4-propyl-pyrazol-1-yl)-5-(2-pyrrolidin-1-yl-ethyl)-5H-1,2,4-triazino[5,6-b]indole;

2-[3-(3,5-dimethyl-4-propyl-pyrazol-1-yl)-1,2,4-triazino[5,6-b]indol-5-yl]-ethanol;

3-[3,5-dimethyl-4-(1-phenyl-ethyl)-pyrazol-1-yl]-5-methyl-5H-1,2,4-triazino[5,6-b]indole;

3-(4-benzhydryl-3,5-dimethyl-pyrazol-1-yl)-5-methyl-5H-1,2,4-triazino[5,6-b]indole;

3-[3,5-dimethyl-4-(1-phenyl-ethyl)-pyrazol-1-yl]-5-ethyl-5H-1,2,4-triazino[5,6-b]indole;

3-(4-benzhydryl-3,5-dimethyl-pyrazol-1-yl)-5-ethyl-5H-1,2,4-triazino[5,6-b]indole;

3-[4-(4-methoxy-phenyl)-pyrazol-1-yl]-5-methyl-5H-1,2,4-triazino[5,6-b]indole;

3-[4-(3-bromo-phenyl)-pyrazol-1-yl]-5-methyl-5H-1,2,4-triazino[5,6-b]indole;

5-methyl-3-(4-quinolin-4-yl-pyrazol-1-yl)-5H-1,2,4-triazino[5,6-b]indole;

5-methyl-3-(4-pyridin-2-yl-pyrazol-1-yl)-5H-1,2,4-triazino[5,6-b]indole;

3-[4-(4-bromo-phenyl)-pyrazol-1-yl]-5-methyl-5H-1,2,4-triazino[5,6-b]indole;

3-(3,5-dimethyl-4-propyl-pyrazol-1-yl)-5-[2-(tetrahydro-pyran-2-yloxy)-ethyl]-5H-1,2,4-triazino[5,6-b]indole;

5-[2-(tetrahydro-pyran-2-yloxy)-ethyl]-3-(3,4,5-trimethyl-pyrazol-1-yl)-5H-1,2,4-triazino[5,6-b]indole;

3-(4-benzyl-3,5-dimethyl-pyrazol-1-yl)-5-[2-(tetrahydro-pyran-2-yloxy)-ethyl]-5H-1,2,4-triazino[5,6-b]indole;

3-(4-ethyl-3,5-dimethyl-pyrazol-1-yl)-5-[2-(tetrahydro-pyran-2-yloxy)-ethyl]-5H-1,2,4-triazino[5,6-b]indole; and

2-[3-(4-benzyl-3,5-dimethyl-pyrazol-1-yl)-1,2,4-triazino[5,6-b]indol-5-yl]-ethanol.

Alternative names for the first three compounds listed above are, respectively:

5-methyl-3-(5-methyl-3-phenyl-pyrazol-1-yl)-5*H*-1,2,4-triazino[5,6-*b*]indole;

3-(3,5-dimethyl-4-propyl-pyrazol-1-yl)-5-methyl-5*H*-1,2,4-triazino[5,6-*b*]indole; and

5-amino-1-(5-methyl-5*H*-1,2,4-triazino[5,6-*b*]indol-3-yl)-1H-pyrazole-4-carboxylic acid ethyl ester.

Compounds of the invention may be chiral. They may be in the form of a single enantiomer or diastereomer, or a racemate.

The compounds of the invention may be prepared in racemic form, or prepared in individual enantiomeric form by specific synthesis or resolution as will be appreciated in the art. The compounds may, for example, be resolved into their enantiomers by standard techniques, such as the formation of diastereomeric pairs by salt formation with an optically active acid followed by fractional crystallisation and regeneration of the free base. Alternatively, the enantiomers of the novel compounds may be separated by HPLC using a chiral column.

A compound of the invention may be in a protected amino, protected hydroxy or protected carboxy form. The terms "protected amino", "protected hydroxy" and "protected carboxy" as used herein refer to amino, hydroxy and carboxy groups which are protected in a manner familiar to those skilled in the art. For example, an amino group can be protected by a benzyloxycarbonyl, tert-butoxycarbonyl, acetyl or like group, or in the form of a phthalimido or like group. A carboxyl group can be protected in the form of a readily cleavable ester such as the methyl, ethyl, benzyl or tert-butyl ester. A hydroxy group can be protected by an alkyl or like group.

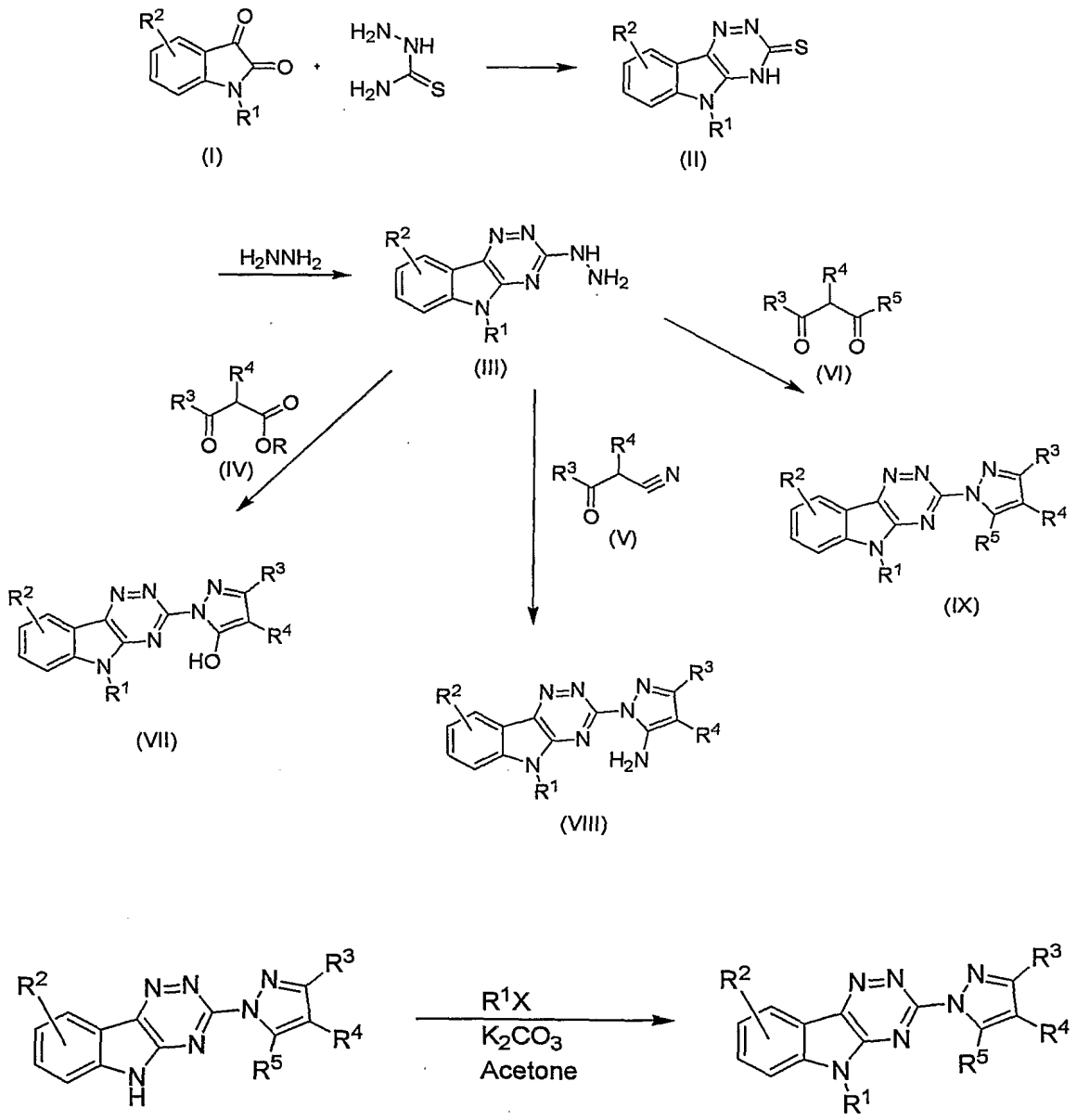
Some compounds of the formula may exist in the form of solvates, for example hydrates, which also fall within the scope of the present invention.

Compounds of the invention may be in the form of pharmaceutically acceptable salts, for example, addition salts of inorganic or organic acids. Such inorganic acid addition salts include, for example, salts of hydrobromic acid, hydrochloric acid, nitric acid, phosphoric acid and sulphuric acid. Organic acid addition salts include, for example, salts of acetic acid, benzenesulphonic acid, benzoic acid, camphorsulphonic acid, citric acid, 2-(4-chlorophenoxy)-2-methylpropionic acid, 1,2-ethanedisulphonic acid, ethanesulphonic acid, ethylenediaminetetraacetic acid (EDTA), fumaric acid, glucoheptonic acid, gluconic acid, glutamic acid, N-glycolylarsanilic acid, 4-hexylresorcinol, hippuric acid, 2-(4-hydroxybenzoyl)benzoic acid, 1-hydroxy-2-naphthoic acid, 3-hydroxy-2-naphthoic acid, 2-hydroxyethanesulphonic acid, lactobionic acid, n-dodecyl sulphuric acid, maleic acid, malic acid, mandelic acid, methanesulphonic acid, methyl sulphuric acid, mucic acid, 2-naphthalenesulphonic acid, pamoic acid, pantothenic acid, phosphanilic acid ((4-aminophenyl)phosphonic acid), picric acid, salicylic acid, stearic acid, succinic acid, tannic acid, tartaric acid, terephthalic acid, p-toluenesulphonic acid, 10-undecenoic acid and the like.

Salts may also be formed with inorganic bases. Such inorganic base salts include, for example, salts of aluminium, bismuth, calcium, lithium, magnesium, potassium, sodium, zinc and the like. Organic base salts include, for example, salts of N, N'-dibenzylethylenediamine, choline (as a counterion), diethanolamine, ethanolamine, ethylenediamine, N,N'-bis(dehydroabietyl)ethylenediamine, N-methylglucamine, procaine, tris(hydroxymethyl)aminomethane ("TRIS") and the like.

It will be appreciated that such salts, provided that they are pharmaceutically acceptable, may be used in therapy. Such salts may be prepared by reacting the compound with a suitable acid or base in a conventional manner.

A compound of the invention may be prepared by any suitable method known in the art and/or by the following processes (in which X is a leaving group such as Cl or Br):



It will be understood that the processes detailed above are solely for the purpose of illustrating the invention and should not be construed as limiting. A process utilising similar or analogous reagents and/or conditions known to one skilled in the art may also be used to obtain a compound of the invention.

Any mixtures of final products or intermediates obtained can be separated on the basis of the physico-chemical differences of the constituents, in a known manner, into the pure final products or intermediates, for example by chromatography, distillation, fractional crystallisation, or by the formation of a

salt if appropriate or possible under the circumstances.

The activity and selectivity of the compounds may be determined by any suitable assay known in the art.

In therapeutic use, the active compound may be administered orally, intravenously, rectally, parenterally, by inhalation (pulmonary delivery), topically, ocularly, nasally, or to the buccal cavity. Oral administration is preferred. Thus, a composition of the present invention may take the form of any of the known pharmaceutical compositions for such methods of administration. The compositions may be formulated in a manner known to those skilled in the art so as to give a controlled release, for example rapid release or sustained release, of the compounds of the present invention. Pharmaceutically acceptable carriers suitable for use in such compositions are well known in the art. The compositions of the invention may contain 0.1-99% by weight of active compound. The compositions of the invention are generally prepared in unit dosage form. Preferably, a unit dose comprises the active ingredient in an amount of 1-500 mg. The excipients used in the preparation of these compositions are the excipients known in the art.

Appropriate dosage levels may be determined by any suitable method known to one skilled in the art. It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors, including the activity of the specific compound employed, the age, body weight, general health and sex of the patient; diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the disease undergoing treatment.

Compositions for oral administration include known pharmaceutical forms for such administration, for example tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups and elixirs. Compositions intended for oral use may be prepared according to any method known to the art. The compositions may contain one or more agents such as sweetening agents, flavouring agents, colouring agents and preserving agents, in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with

non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be, for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example corn starch or alginic acid; binding agents, for example starch gelatin, acacia, microcrystalline cellulose or polyvinyl pyrrolidone; and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin or olive oil.

Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinyl pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally occurring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long-chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids, for example polyoxyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl or n-propyl p-hydroxybenzoate, one or more colouring agents, one or more flavouring agents, and one or more sweetening agents, such as sucrose or saccharin.

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or

in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents, such as those set forth above, and flavouring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an antioxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable sweetening, flavouring and colouring agents may also be present.

The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin, or mixtures of these. Suitable emulsifying agents may be naturally occurring gums, for example gum acacia or gum tragacanth, naturally occurring phosphatides, for example soya bean, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavouring agents.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavouring and colouring agents. The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be in a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending

medium. For this purpose, any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid, find use in the preparation of injectables.

The compounds of the invention may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

Compositions for topical administration may also be suitable for use in the present invention. The active compound may be dispersed in a pharmaceutically acceptable cream, ointment or gel. A suitable cream may be prepared by incorporating the active compound in a topical vehicle such as light liquid paraffin, dispersed in a aqueous medium using surfactants. An ointment may be prepared by mixing the active compound with a topical vehicle such as a mineral oil or wax. A gel may be prepared by mixing the active compound with a topical vehicle comprising a gelling agent. Topically administrable compositions may also comprise a matrix in which the pharmaceutically active compounds of the present invention are dispersed so that the compounds are held in contact with the skin in order to administer the compounds transdermally.

The following Examples illustrate the invention.

In the Examples, analytical hplc was carried out with a Waters 2525 LC pump and Waters Xterra C18 column (5µm, 50mm x 4.6mm). Mobile phases A (0.1% formic acid in 10mM aqueous ammonium acetate) and B (0.1% formic acid in acetonitrile) were used. Elution with 5% B was held for 1 minute, raised to 95% B over 4.5 minutes and held for 1 minute at a flow rate of 2 or 34ml/minute. Photodiode array detection was by a Waters 996, range 210-350nm UV. The mass spectrometer was a Micromass ZQ operating in electrospray ionisation mode.

Intermediate 1: 9-Methyl-1,9-dihydro-1,3,4,9-tetraaza-fluorene-2-thione

See Gladych *et al*, *J. Med. Chem.*, 3, 15, (1972). An alternative name for this compound is 5-Methyl-4,5-dihydro-1,2,4-triazino[5,6-*b*]indole-3-thione.

1-Methyl Isatin (1.0 g, 6.2 mmol), thiosemicarbazide (0.565 g, 6.2 mmol) and potassium carbonate (1.28 g, 9.26 mmol) were suspended in water (40 ml) then brought to reflux. Reflux was maintained for 16 hours. The mixture was then cooled to room temperature, filtered and acidified with glacial acetic acid. The resulting yellow precipitate was filtered and dried under vacuum to give the product, 1.175 g (87.6%), hplc/ms (positive ion) Rt 2.49 min, m/z 217 ($M+H^+$).

Intermediate 2: (9-Methyl-9H-1,3,4,9-tetraaza-fluoren-2-yl)-hydrazine

See Ram, *Arch. Pharm.* (Weinheim), 313, 108-113, (1980). An alternative name for this compound is (5-Methyl-5*H*-1,2,4-triazino[5,6-*b*]indol-3-yl)-hydrazine

A solution of Intermediate 1 (0.4 g, 1.85 mmol) in hydrazine hydrate (4 ml) was refluxed for 4 hours. On cooling, the yellow precipitate was filtered, washed with water (10 ml), then methanol (2 ml) and dried under vacuum to give the product, 0.298 g (75.1%), NMR (d6-DMSO) δ (300MHz): 3.7 (s, 3H); 4.4 (bs, 2H); 7.35 (t, 1H); 7.55 (m, 2H); 8.1 (d, 1H); 8.7 (bs, 1H).

Intermediate 3: 4,5-dihydro-1,2,4-triazino[5,6-*b*]indole-3-thione

Isatin (10 g, 68 mmol), thiosemicarbazide (6.2 g, 68 mmol) and potassium carbonate (14.1 g, 102 mmol) were suspended in water (340 ml) then brought to reflux. Reflux was maintained for 16 hours. The mixture was cooled to room temperature, filtered and the solid washed with water (50 ml). The solid was dried under vacuum to give the product, 4.5 g (33%), as a yellow solid, hplc/ms (positive ion) Rt 2.7 min, m/z 203 ($M+H^+$).

Intermediate 4: (5*H*-1,2,4-triazino[5,6-*b*]indol-3-yl)-hydrazine

In a manner analogous to that of Intermediate 2, using Intermediate 3 (1.0 g, 4.95 mmol) in place of Intermediate 1, was prepared the title compound (0.99 g, 100%) as a yellow solid, hplc/ms (positive ion) Rt 1.41 min, m/z 201 ($M+H^+$).

Intermediate 5: 3-benzyl-pentane-2,4-dione

Oven-dried alumina (5 g, 50 mmol) was stirred with a 1M solution of potassium tert-butoxide in tetrahydrofuran (5 ml, 5 mmol) under nitrogen for 10 minutes. Solvent was evaporated under vacuo to give a free-flowing solid. The vigorously stirred solid under nitrogen was treated dropwise with pentane-2,4-dione (501 mg, 5 mmol). After stirring for 40 minutes the mixture was treated

with benzyl bromide (855 mg, 5 mmol) and stirred for 5 hours. The solid was applied to a short silica gel column and eluted with dichloromethane. The eluate was concentrated and the residue purified by flash chromatography eluting with 10% ethyl acetate/hexane. Concentration of product-containing fractions gave the title compound (375 mg, 40%) Rf (10% ethyl acetate/hexane) 0.3; NMR (CDCl3) δ (300MHz): 2.05 (s, 4.8H); 2.1 (s, 1.2H); 3.1 (d, 0.4H); 3.7 (s, 1.6H); 4.0 (t, 0.2H); 7.0-7.4 (m, 5H) [mixture of keto and enol forms].

Intermediate 6: 3-(2-benzyloxy-benzyl)-pentane-2,4-dione

A mixture of 2-benzyloxy benzyl alcohol (2.57 g, 12 mmol), chlorodiphenylphosphine (3.5 g, 16 mmol) and imidazole (1.85 g, 27 mmol) were stirred in toluene (150 ml) under nitrogen. A solution of iodine (4.06 g, 16 mmol) in toluene (50 ml) was added dropwise over 15 minutes and the reaction mixture stirred at room temperature for 30 minutes. The reaction mixture was poured into saturated aqueous sodium bicarbonate (300 ml) and the layers separated. The organic phase was washed with saturated aqueous sodium thiosulphate (100 ml), then water (100 ml) and dried over sodium sulphate, filtered and evaporated. The residue was subjected to chromatography on silica gel eluted with dichloromethane. Evaporation of product containing fractions gave 1-benzyloxy-2-iodomethyl-benzene (3.33 g, 86%) as a red oil.

A solution of 1-benzyloxy-2-iodomethyl benzene (3.24 g, 10 mmol) in methyl ethyl ketone (20 ml) was treated with sodium acetyl acetonate (1.23 g, 10 mmol). The mixture was heated at reflux for 1 hour then evaporated to dryness. Water (40 ml) was added and extracted with diethyl ether (3 x 20 ml). The combined extracts were concentrated and the residue subjected to chromatography on silica gel eluted with hexane for 2 minutes then a gradient to 25% ethyl acetate/hexane over 15 minutes. Evaporation of product containing fractions gave the title compound (1.79 g, 60%) as a clear oil. NMR (CDCl3) δ (300MHz): 2.02 (s, 3H); 2.05 (s, 3H); 3.1 (d, 1H); 3.7 (s, 1H); 4.1 (t, 0.5H); 5.1 (d, 2H); 6.8-7.4 (m, 9H) [mixture of keto and enol forms].

Intermediate 7: 3-(4-benzyloxy-benzyl)-pentane-2,4-dione

In a manner analogous to Example 6, using 4-benzyloxy-benzyl alcohol (8 g, 37 mmol) in place of 2-benzyloxy-benzyl alcohol, was prepared the title

compound (1.41g, 19%) as a clear oil. NMR (CDCl3) δ (300MHz): 2.05 (s, 3H); 2.1 (s, 3H); 3.1 (d, 1H); 3.7 (s, 1H); 4.0 (t, 0.5H); 5.1 (d, 2H); 6.8-7.4 (m, 9H) [mixture of keto and enol forms].

Intermediate 8: 3-(4-hydroxy-benzyl)-pentane-2,4-dione

A solution of Intermediate 7 (1.4 g, 4.7 mmol) in methanol (20 ml) was hydrogenated over 10% palladium on carbon at atmospheric pressure for 2 hours. The suspension was filtered, the filtrate concentrated and the residue purified by flash chromatography on silica gel eluted with 1:1 ethyl acetate hexane to give the title compound (310 mg, 32%). NMR (CDCl3) δ (300MHz): 2.05 (s, 2H); 2.1 (s, 4H); 3.1 (d, 1.3H); 3.6 (s, 0.7H); 4.0 (t, 0.7H); 6.8-7.0 (2q, 4H) [mixture of keto and enol forms].

Intermediate 9: 3-(2-hydroxy-benzyl)-pentane-2,4-dione

In a manner analogous to Intermediate 8, starting from 3-(2-benzyloxy-benzyl)-pentane-2,4-dione (Intermediate 6, 350 mg, 1.18 mmol), was obtained the title compound (210 mg, 86%).

Intermediate 10: 3-(3-benzyloxy-benzyl)-pentane-2,4-dione

In a manner analogous to Intermediate 6, using 3-benzyloxy-benzyl alcohol (2.57 g, 12 mmol) in place of 2-benzyloxy-benzyl alcohol, was prepared the title compound (1.9g, 53%) as a clear oil.

Intermediate 11: 3-(3-hydroxy-benzyl)-pentane-2,4-dione

In a manner analogous to Intermediate 8, starting from 3-(3-benzyloxy-benzyl)-pentane-2,4-dione (Intermediate 10, 1.9 g, 6.4 mmol), was prepared the title compound (400 mg, 30%).

Intermediate 12: 3-(3,5-dimethoxy-benzyl)-pentane-2,4-dione

In a manner analogous to Intermediate 5, starting from 3,5-dimethoxy-benzyl bromide (878 mg, 3.8 mmol), was prepared the title compound (189 mg, 30%).

Intermediate 13: 3-naphthalen-2-ylmethyl-pentane-2,4-dione

In a manner analogous to Intermediate 5, starting from 2-bromomethyl naphthalene (840 mg, 3.8 mmol), was prepared the title compound (376 mg,

41%). NMR (CDCl3) δ (300MHz): 2.05 (s, 5H); 2.1 (s, 1H); 3.2 (d, 0.3H); 3.9 (s, 1.7H); 4.1 (t, 0.15H); 7.3-7.9 (m, 7H) [mixture of keto and enol forms].

Intermediate 14: 3-(2-fluoro-benzyl)-pentane-2,4-dione

In a manner analogous to Intermediate 5, starting from 2-fluoro-benzyl bromide (718 mg, 3.8 mmol), was prepared the title compound (374 mg, 47%). NMR (CDCl3) δ (300MHz): 2.05 (s, 4.6H); 2.1 (s, 1.4H); 3.1 (d, 0.45H); 3.7 (s, 1.55H); 4.05 (t, 0.22H); 7.0-7.3 (m, 4H) [mixture of keto and enol forms].

Intermediate 15: 3-(3-trifluoromethyl-benzyl)-pentane-2,4-dione

In a manner analogous to Intermediate 5, starting from 3-trifluoromethyl-benzyl bromide (778 mg, 4 mmol), was prepared the title compound (412 mg, 40%).

Intermediate 16: 3-(2-methoxy-benzyl)-pentane-2,4-dione

A mixture of sodium acetyl acetonate (1.0 g, 7.14 mmol) and 2-methoxy-benzyl chloride (1 ml, 7.14 mmol) in methyl ethyl ketone (10 ml) was heated at reflux under nitrogen for 2 hours. Solvent was evaporated and the residue extracted with diethyl ether (3 x 100 ml). The combined extracts were dried over sodium sulphate, filtered and evaporated. Flash chromatography on silica gel eluted with a gradient of 5% ethyl acetate/hexane to 25% ethyl acetate/hexane over 25 minutes and concentration of product containing fractions gave the title compound (873 mg, 56%).

Intermediate 17: 3-(3-fluoro-benzyl)-pentane-2,4-dione

In a manner analogous to Intermediate 5, starting from 3-fluoro-benzyl bromide (718 mg, 3.8 mmol), was prepared the title compound (292 mg, 37%). NMR (CDCl3) δ (300MHz): 2.05 (s, 4.5H); 2.1 (s, 1.5H); 3.1 (d, 0.5H); 3.7 (s, 1.5H); 4.0 (t, 0.25H); 6.7-7.3 (m, 4H) [mixture of keto and enol forms].

Intermediate 18: 3-(3-methoxy-benzyl)-pentane-2,4-dione

In a manner analogous to Intermediate 5, starting from 3-methoxy-benzyl bromide (764 mg, 3.8 mmol), was prepared the title compound (460 mg, 55%). NMR (CDCl3) δ (300MHz): 2.05 (s, 4.5H); 2.1 (s, 1.5H); 3.1 (d, 0.5H); 3.7 (s, 1.5H); 3.9 (s, 3H); 4.0 (t, 0.25H); 6.7-7.3 (m, 4H) [mixture of keto and enol forms].

Intermediate 19: 3-(2-nitro-benzyl)-pentane-2,4-dione

In a manner analogous to Intermediate 5, starting from 2-nitro-benzyl bromide (821 mg, 3.8 mmol), was prepared the title compound (376 mg, 42%). NMR (CDCl3) δ (300MHz): 2.05 (s, 4H); 2.2 (s, 2H); 3.4 (d, 0.7H); 4.0 (s, 1.3H); 4.1 (t, 0.35H); 7.3-8.0 (m, 4H) [mixture of keto and enol forms].

Intermediate 20: 3-(4-methoxy-benzyl)-pentane-2,4-dione

In a manner analogous to Intermediate 5, starting from 4-methoxy-benzyl chloride (625 mg, 4 mmol), was prepared the title compound (315 mg, 36%). NMR (CDCl3) δ (300MHz): 2.05 (s, 4.4H); 2.1 (s, 1.6H); 3.1 (d, 0.5H); 3.6 (s, 1.5H); 3.8 (s, 3H); 3.9 (t, 0.25H); 6.8-7.1 (2q, 4H) [mixture of keto and enol forms].

Intermediate 21: 3-(4-nitro-benzyl)-pentane-2,4-dione

In a manner analogous to Intermediate 5, starting from 4-nitro-benzyl bromide (821 mg, 3.8 mmol), was prepared the title compound (213 mg, 24%). NMR (CDCl3) δ (300MHz): 2.05 (s, 4H); 2.15 (s, 2H); 3.2 (d, 0.66H); 3.8 (s, 1.34H); 4.0 (t, 0.33H); 7.3 (m, 2H); 8.2 (m, 2H) [mixture of keto and enol forms].

Intermediate 22: 3-(4-trifluoromethyl-benzyl)-pentane-2,4-dione

In a manner analogous to Intermediate 5, starting from 4-trifluoromethyl-benzyl chloride (821 mg, 4 mmol), was prepared the title compound (300 mg, 29%). NMR (CDCl3) δ (300MHz): 2.05 (s, 3.3H); 2.1 (s, 2.7H); 3.2 (d, 1H); 3.8 (s, 1H); 4.0 (t, 0.5H); 7.3 (m, 2H); 7.5 (m, 2H) [mixture of keto and enol forms].

Intermediate 23: 3-(4-methanesulphonyl-benzyl)-pentane-2,4-dione

In a manner analogous to Intermediate 5, starting from 4-methanesulphonyl-benzyl bromide (996 mg, 4 mmol), was prepared the title compound (350 mg, 33%). NMR (CDCl3) δ (300MHz): 2.05 (s, 4H); 2.1 (s, 2H); 3.05 (2s, 3H); 3.2 (d, 0.66H); 3.8 (s, 1.34H); 4.0 (t, 0.33H); 7.4 (m, 2H); 7.9 (m, 2H) [mixture of keto and enol forms].

Intermediate 24: 3-(2-trifluoromethyl-benzyl)-pentane-2,4-dione

In a manner analogous to Intermediate 5, starting from 2-trifluoromethyl-benzyl bromide (778 mg, 3.2 mmol), was prepared the title compound (200 mg, 24%).

Intermediate 25: 3-(2-methyl-benzyl)-pentane-2,4-dione

In a manner analogous to Intermediate 5, starting from 2-methyl-benzyl bromide (740 mg, 4 mmol), was prepared the title compound (656 mg, 80%). NMR (CDCl3) δ (300MHz): 2.0 (s, 3H); 2.1 (s, 3H); 2.25 (2s, 3H); 3.1 (d, 1H); 3.6 (s, 1H); 4.0 (t, 0.5H); 6.9 – 7.2 (m, 4H) [mixture of keto and enol forms].

Intermediate 26: 3-(3-methyl-benzyl)-pentane-2,4-dione

In a manner analogous to Intermediate 5, starting from 2-methyl-benzyl bromide (740 mg, 4 mmol), was prepared the title compound (509 mg, 62%). NMR (CDCl3) δ (300MHz): 2.05 (s, 3H); 2.1 (s, 3H); 2.3 (2s, 3H); 3.1 (d, 1H); 3.6 (s, 1H); 4.0 (t, 0.5H); 6.9 – 7.2 (m, 4H) [mixture of keto and enol forms].

Intermediate 27: 3-phenethyl-pentane-2,4-dione

In a manner analogous to Intermediate 5, starting from 2-bromoethyl benzene (740 mg, 4 mmol), was prepared the title compound (601 mg, 74%).

Intermediate 28: 4-(2-acetyl-3-oxo-butyl)-benzoic acid methyl ester

In a manner analogous to Intermediate 5, starting from 4-bromomethyl benzoic acid methyl ester (1.83 g, 8 mmol), was prepared the title compound (680 mg, 34%). NMR (CDCl3) δ (300MHz): 2.05 (s, 3.3H); 2.1 (s, 2.7H); 3.2 (d, 0.8H); 3.75 (s, 1.2H); 3.9 (2s, 3H); 4.0 (t, 0.4H); 7.2 (m, 2H); 8.0 (m, 2H) [mixture of keto and enol forms].

Intermediate 29: 3-(2-acetyl-3-oxo-butyl)-benzoic acid methyl ester

In a manner analogous to Intermediate 5, starting from 3-bromomethyl benzoic acid methyl ester (916 mg, 8 mmol), was prepared the title compound (332 mg, 33%). NMR (CDCl3) δ (300MHz): 2.05 (s, 3H); 2.1 (s, 3H); 3.2 (d, 1H); 3.75 (s, 1H); 3.9 (s, 3H); 4.0 (t, 0.5H); 7.35 (m, 2H); 7.9 (m, 2H) [mixture of keto and enol forms].

Intermediate 30: 5-ethyl-4,5-dihydro-1,2,4-triazino[5,6-*b*]indole-3-thione

In a manner analogous to Intermediate 3, using 1-ethyl-1*H*-indole-2,3-dione (2.29 g, 13 mmol) in place of isatin, was prepared the title compound (2.63 g, 88%). NMR (d6-DMSO) δ (300MHz): 1.5 (t, 3H); 4.25 (q, 2H); 7.5 (m, 1H); 7,75 (m, 2H); 8.1 (d, 1H).

The 1-ethyl-1*H*-indole-2,3-dione used as the starting material was prepared as follows.

Isatin (3 g, 20 mmol), potassium carbonate (5.6 g, 40 mmol) and iodomethane (3.43 g, 22 mmol) were stirred in tetrahydrofuran (100 ml) under nitrogen and treated with tetra-n-butyl ammonium hydrogen sulphate (100 mg). The mixture was heated at reflux, cooled to room temperature and the solvent evaporated. The residue was partitioned between dichloromethane (100 ml) and water (100 ml). The aqueous phase was extracted with dichloromethane (2 x 50 ml) and the combined organic fractions treated with activated charcoal, filtered and concentrated. Crystallisation of the residue from dichloromethane/hexane gave 1-ethyl-1*H*-indole-2,3-dione (2.97 g) in two crops. Hplc/ms (positive ion) Rt 2.89 min, m/z 176 ($M+H^+$).

Intermediate 31: (5-ethyl-5*H*-1,2,4-triazino[5,6-*b*]indol-3-yl)-hydrazine

In a manner analogous to Intermediate 4, using 5-ethyl-4,5-dihydro-1,2,4-triazino[5,6-*b*]indole-3-thione (Intermediate 30, 1 g, 4.34 mmol), was prepared the title compound (907 mg, 91%). Hplc/ms (positive ion) Rt 2.25 min, m/z 229 ($M+H^+$).

Intermediate 32: 3-(4-fluoro-benzyl)-pentane-2,4-dione

In a manner analogous to Intermediate 5, starting from 4-fluorobenzyl bromide (718 mg, 3.8 mmol), was prepared the title compound (273 mg, 35%). NMR (CDCl3) δ (300MHz): 2.05 (s, 4.3H); 2.1 (s, 1.7H); 3.2 (d, 0.5H); 3.75 (s, 1.5H); 4.0 (t, 0.25H); 6.9 – 7.1 (m, 4H) [mixture of keto and enol forms].

Intermediate 33: 3-(3-nitro-benzyl)-pentane-2,4-dione

In a manner analogous to Intermediate 5, starting from 3-nitro-benzyl bromide (821 mg, 3.8 mmol), was prepared the title compound (231 mg, 26%). NMR (CDCl3) δ (300MHz): 2.05 (s, 4.3H); 2.1 (s, 1.7H); 3.2 (d, 0.5H); 3.75 (s, 1.5H); 4.0 (t, 0.25H); 6.9 – 7.1 (m, 4H) [mixture of keto and enol forms].

Intermediate 34: 3-(1-phenyl-ethyl)-pentane-2,4-dione

In a manner analogous to Intermediate 5, starting from (1-bromoethyl)-benzene (740 mg, 4 mmol), was prepared the title compound (200 mg, 25%). NMR (CDCl3) δ (300MHz): 1.2 (d, 1.5H); 1.5 (d, 1.5H); 1.85 (s, 3H); 2.27 (s, 3H); 3.6 (m, 0.5H); 4.05 (d, 0.5H); 4.95 (m, 0.5H); 7.15-7.4 (m, 5H) [mixture of keto and enol forms].

Intermediate 35: 3-benzhydryl-pentane-2,4-dione

In a manner analogous to Intermediate 5, starting from benzhydryl bromide (989 mg, 4 mmol), was prepared the title compound (300 mg, 28%).

Example 1: 9-Methyl-2-(5-methyl-3-phenyl-pyrazol-1-yl)-9H-1,3,4,9-tetraaza-fluorene

To a stirred solution of Intermediate 2 (10mg, 0.0466 mmol) and benzoylacetone (37.3mg, 0.23 mmol) in anhydrous ethanol (1 ml), was added one drop of glacial acetic acid. The mixture was then heated to 140°C in a sealed vial under microwave conditions for 4 minutes. On cooling, 2 drops of aqueous ammonia were added and the resulting precipitate was filtered and dried under vacuum to give the product as a yellow solid, 5.19 mg (33.1%), hplc/ms (positive ion) Rt 4.21 min, m/z 341 ($M+H^+$).

Example 2: 2-(3,5-Dimethyl-4-propyl-pyrazol-1-yl)-9-methyl-9H-1,3,4,9-tetraaza-fluorene

To a stirred solution of Intermediate 2 (10mg, 0.0466 mmol) and 3-propyl-2,4-pentanedione (32.7 mg, 0.23 mmol) in anhydrous ethanol (1 ml) was added one drop of glacial acetic acid. The mixture was then heated to 140°C in a sealed vial under microwave conditions for 5 minutes. On cooling, the resulting precipitate was filtered and dried under vacuum to give the product as a yellow solid, 6.60 mg (44.8%), hplc/ms (positive ion) Rt 4.41 min, m/z 321 ($M+H^+$).

Example 3: 5-Amino-1-(9-methyl-9H-1,3,4,9-tetraaza-fluoren-2-yl)-1H-pyrazole-4-carboxylic acid ethyl ester

A solution of Intermediate 2 (10mg, 0.0466 mmol) and 2-cyano-3-ethoxy-acrylic acid ethyl ester (10 mg, 0.082 mmol) in anhydrous ethanol (1 ml) was heated to 140°C in a sealed vial under microwave conditions for 5 minutes. On cooling, the resulting precipitate was filtered and dried under vacuum to give the product as a yellow solid, 12.85mg (81.7%), hplc/ms (positive ion) Rt 3.47 min, m/z 338 ($M+H^+$).

Example 4:3-(4-ethyl-3,5-dimethyl-pyrazol-1-yl)-5*H*-1,2,4-triazino[5,6-*b*] indole

A solution of (5*H*-1,2,4-triazino[5,6-*b*]indol-3-yl)-hydrazine (Intermediate 4 , 100 mg, 0.5 mmol) in 20% acetic acid/ethanol (2 ml) was treated with 3-ethyl-pentane-2,4-dione (320 mg, 2.5 mmol) and heated to 140°C in a sealed vial under microwave conditions for 5 minutes. On cooling, the resulting precipitate was filtered and dried under vacuum to give the product (50 mg, 34%) as a pale yellow solid, hplc/ms (positive ion) Rt 3.77 min, m/z 293 ($M+H^+$).

Example 5: 3-(4-benzyl-3,5-dimethyl-pyrazol-1-yl)-5*H*-1,2,4-triazino[5,6-*b*]indole

A solution of (5*H*-1,2,4-triazino[5,6-*b*]indol-3-yl)-hydrazine (Intermediate 4, 200 mg, 1 mmol) in 20% acetic acid/ethanol (3 ml) was treated with 3-benzyl-pentane-2,4-dione (Intermediate 5, 950 mg, 5 mmol) and heated to 140°C in a sealed vial under microwave conditions for 20 minutes. The reaction mixture was cooled to room temperature and filtered. The solid was washed with ethanol (2 ml) and dried in vacuo to give the product (180 mg, 51%) as a pale yellow solid, hplc/ms (negative ion) Rt 4.17 min, m/z 353 ($M-H^-$).

Example 6: 3-[4-(2-benzyloxy-benzyl)-3,5-dimethyl-pyrazol-1-yl]-5*H*-1,2,4-triazino[5,6-*b*]indole

In a manner analogous to that of Example 5, using Intermediate 4 (10 mg, 50 µmol) and Intermediate 6 (50 mg, 170 µmol) was prepared the title compound (5 mg, 22%) as a pale yellow solid after preparative hplc. Hplc/ms (negative ion) Rt 4.79 min, m/z 459 ($M-H^-$).

Example 7: 4-[3,5-dimethyl-1-(5*H*-1,2,4-triazino[5,6-*b*]indol-3-yl)-1*H*-pyrazol-4-ylmethyl]-phenol

A solution of (5*H*-1,2,4-triazino[5,6-*b*]indol-3-yl)-hydrazine (Intermediate 4, 10 mg, 50 µmol) in 20% acetic acid/ethanol (1 ml) was treated with 3-(4-hydroxy-benzyl)-pentane-2,4-dione (Intermediate 8, 30 mg, 145 µmol) and heated to 140°C in a sealed vial under microwave conditions for 20 minutes. The reaction mixture was cooled, diluted with water (1 ml) and the suspension

filtered. The solid was dried to give the title compound (14 mg, 76%). Hplc/ms (negative ion) Rt 3.56 min, m/z 369 ($M-H^-$).

Example 8: 2-[3,5-dimethyl-1-(5*H*-1,2,4-triazino[5,6-*b*]indol-3-yl)-1*H*-pyrazol-4-ylmethyl]-phenol

In a manner analogous to Example 7, using Intermediate 9 in place of Intermediate 8, was prepared the title compound (14 mg, 76%). Hplc/ms (negative ion) Rt 3.69 min, m/z 369 ($M-H^-$).

Example 9: 3-[3,5-dimethyl-1-(5*H*-1,2,4-triazino[5,6-*b*]indol-3-yl)-1*H*-pyrazol-4-ylmethyl]-phenol

In a manner analogous to Example 7, using Intermediate 11 in place of Intermediate 8, was prepared the title compound (15 mg, 81%). Hplc/ms (negative ion) Rt 3.64 min, m/z 369 ($M-H^-$).

Example 10: 3-[4-(3,5-dimethoxy-benzyl)-3,5-dimethyl-pyrazol-1-yl]-5*H*-1,2,4-triazino[5,6-*b*]indole

In a manner analogous to Example 5, using Intermediate 4 (8.8 mg, 44 µmol) and Intermediate 12 (33 mg, 132 µmol), was prepared the title compound (14 mg, 77%). Hplc/ms (negative ion) Rt 4.12 min, m/z 413 ($M-H^-$).

Example 11: 3-(3,5-dimethyl-4-naphthalen-2-ylmethyl-pyrazol-1-yl)-5*H*-1,2,4-triazino[5,6-*b*]indole

In a manner analogous to Example 5, using Intermediate 4 (50 mg, 250 µmol) and Intermediate 13 (180 mg, 750 µmol), was prepared the title compound (64 mg, 63%). Hplc/ms (negative ion) Rt 4.59 min, m/z 403 ($M-H^-$).

Example 12: 3-[4-(2-fluoro-benzyl)-3,5-dimethyl-pyrazol-1-yl]-5*H*-1,2,4-triazino[5,6-*b*]indole

In a manner analogous to Example 5, using Intermediate 4 (50 mg, 250 µmol) and Intermediate 14 (156 mg, 750 µmol), was prepared the title compound (40 mg, 43%). Hplc/ms (negative ion) Rt 4.26 min, m/z 371 ($M-H^-$).

Example 13: 3-[3,5-dimethyl-4-(3-trifluoromethyl-benzyl)-pyrazol-1-yl]-5*H*-1,2,4-triazino[5,6-*b*]indole

In a manner analogous to Example 5, using Intermediate 4 (50 mg, 250 µmol) and Intermediate 15 (193 mg, 750 µmol), was prepared the title compound

(40 mg, 38%). Hplc/ms (negative ion) Rt 4.53 min, m/z 421 ($M-H^-$).

Example 14: 3-[4-(2-methoxy-benzyl)-3,5-dimethyl-pyrazol-1-yl]-5-methyl-5*H*-1,2,4-triazino[5,6-*b*]indole

In a manner analogous to Example 5, using Intermediate 2 (10 mg, 47 µmol) and Intermediate 16 (51 mg, 232 µmol), was prepared the title compound (17 mg, 90%). Hplc/ms (positive ion) Rt 4.34 min, m/z 399 ($M+H^+$).

Example 15: 3-[4-(3-fluoro-benzyl)-3,5-dimethyl-pyrazol-1-yl]-5-methyl-5*H*-1,2,4-triazino[5,6-*b*]indole

In a manner analogous to Example 5, using Intermediate 2 (9.4 mg, 44 µmol) and Intermediate 17 (46 mg, 220 µmol), was prepared the title compound (3 mg, 18%). Hplc/ms (positive ion) Rt 4.45 min, m/z 387 ($M+H^+$).

Example 16: 3-[4-(3-methoxy-benzyl)-3,5-dimethyl-pyrazol-1-yl]-5-methyl-5*H*-1,2,4-triazino[5,6-*b*]indole

In a manner analogous to Example 5, using Intermediate 2 (9.4 mg, 44 µmol) and Intermediate 18 (48 mg, 220 µmol), was prepared the title compound (7 mg, 40%). Hplc/ms (positive ion) Rt 4.34 min, m/z 399 ($M+H^+$).

Example 17: 3-[4-(3,5-dimethoxy-benzyl)-3,5-dimethyl-pyrazol-1-yl]-5-methyl-5*H*-1,2,4-triazino[5,6-*b*]indole

In a manner analogous to Example 5, using Intermediate 2 (9.4 mg, 44 µmol) and Intermediate 18 (48 mg, 220 µmol), was prepared the title compound (7 mg, 40%). Hplc/ms (positive ion) Rt 4.34 min, m/z 399 ($M+H^+$).

Example 18: 3-[3,5-dimethyl-4-(2-nitro-benzyl)-pyrazol-1-yl]-5-methyl-5*H*-1,2,4-triazino[5,6-*b*]indole

In a manner analogous to Example 5, using Intermediate 2 (9.4 mg, 44 µmol) and Intermediate 18 (52 mg, 220 µmol), was prepared the title compound (9 mg, 50%). Hplc/ms (positive ion) Rt 4.3 min, m/z 414 ($M+H^+$).

Example 19: 3-[4-(2-fluoro-benzyl)-3,5-dimethyl-pyrazol-1-yl]-5-methyl-5*H*-1,2,4-triazino[5,6-*b*]indole

In a manner analogous to Example 5, using Intermediate 2 (9.4 mg, 44 µmol) and Intermediate 14 (46 mg, 220 µmol), was prepared the title compound (12 mg, 70%). Hplc/ms (positive ion) Rt 4.47 min, m/z 387 ($M+H^+$).

Example 20: 2-[3,5-dimethyl-1-(5-methyl-5*H*-1,2,4-triazino[5,6-*b*]indol-3-yl)-1*H*-pyrazol-4-ylmethyl]-phenol

In a manner analogous to Example 5, using Intermediate 2 (10 mg, 47 µmol) and Intermediate 14 (30 mg, 145 µmol), was prepared the title compound (5 mg, 28%). Hplc/ms (positive ion) Rt 3.85 min, m/z 385 ($M+H^+$).

Example 21: 3-[4-(4-methoxy-benzyl)-3,5-dimethyl-pyrazol-1-yl]-5-methyl-5*H*-1,2,4-triazino[5,6-*b*]indole

In a manner analogous to Example 5, using Intermediate 2 (9.4 mg, 44 µmol) and Intermediate 20 (48 mg, 219 µmol), was prepared the title compound (6 mg, 34%). Hplc/ms (positive ion) Rt 4.34 min, m/z 399 ($M+H^+$).

Example 22: 3-[4-(2-benzyloxy-benzyl)-3,5-dimethyl-pyrazol-1-yl]-5-methyl-5*H*-1,2,4-triazino[5,6-*b*]indole

In a manner analogous to Example 5, using Intermediate 2 (10 mg, 47 µmol) and Intermediate 6 (50 mg, 168 µmol), was prepared the title compound (7 mg, 31%). Hplc/ms (positive ion) Rt 5.02 min, m/z 475 ($M+H^+$).

Example 23: 3-(3,5-dimethyl-4-naphthalen-2-ylmethyl-pyrazol-1-yl)-5-methyl-5*H*-1,2,4-triazino[5,6-*b*]indole

In a manner analogous to Example 5, using Intermediate 2 (9.4 mg, 44 µmol) and Intermediate 13 (53 mg, 219 µmol), was prepared the title compound (5 mg, 27%). Hplc/ms (positive ion) Rt 4.83 min, m/z 419 ($M+H^+$).

Example 24: 3-[3,5-dimethyl-4-(4-nitro-benzyl)-pyrazol-1-yl]-5-methyl-5*H*-1,2,4-triazino[5,6-*b*]indole

In a manner analogous to Example 5, using Intermediate 2 (9.4 mg, 44 µmol) and Intermediate 21 (52 mg, 219 µmol), was prepared the title compound (2.3 mg, 13%). Hplc/ms (positive ion) Rt 4.33 min, m/z 414 ($M+H^+$).

Example 25: 4-[3,5-dimethyl-1-(5-methyl-5*H*-1,2,4-triazino[5,6-*b*]indol-3-yl)-1*H*-pyrazol-4-ylmethyl]-phenol

In a manner analogous to Example 5, using Intermediate 2 (10 mg, 47 µmol) and Intermediate 8 (30 mg, 145 µmol), was prepared the title compound (14 mg, 77%). Hplc/ms (positive ion) Rt 3.7 min, m/z 385 ($M+H^+$).

Example 26: 3-[3,5-dimethyl-1-(5-methyl-5*H*-1,2,4-triazino[5,6-*b*]indol-3-yl)-1*H*-pyrazol-4-ylmethyl]-phenol

In a manner analogous to Example 5, using Intermediate 2 (10 mg, 47 µmol) and Intermediate 11 (30 mg, 145 µmol), was prepared the title compound (14.5 mg, 80%). Hplc/ms (positive ion) Rt 3.8 min, m/z 385 ($M+H^+$).

Example 27: 3-[3,5-dimethyl-4-(4-trifluoromethyl-benzyl)-pyrazol-1-yl]-5-methyl-5*H*-1,2,4-triazino[5,6-*b*]indole

In a manner analogous to Example 5, using Intermediate 2 (9.4 mg, 44 µmol) and Intermediate 22 (34 mg, 132 µmol), was prepared the title compound (10 mg, 52%). Hplc/ms (positive ion) Rt 4.77 min, m/z 437 ($M+H^+$).

Example 28: 3-[4-(4-methanesulphonyl-benzyl)-3,5-dimethyl-pyrazol-1-yl]-5-methyl-5*H*-1,2,4-triazino[5,6-*b*]indole

In a manner analogous to Example 5, using Intermediate 2 (9.4 mg, 44 µmol) and Intermediate 23 (35 mg, 132 µmol), was prepared the title compound (10 mg, 51%). Hplc/ms (positive ion) Rt 3.7 min, m/z 447 ($M+H^+$).

Example 29: 3-[3,5-dimethyl-4-(2-trifluoromethyl-benzyl)-pyrazol-1-yl]-5-methyl-5*H*-1,2,4-triazino[5,6-*b*]indole

In a manner analogous to Example 5, using Intermediate 2 (9.4 mg, 44 µmol) and Intermediate 24 (34 mg, 132 µmol), was prepared the title compound (7 mg, 36%). Hplc/ms (positive ion) Rt 4.85 min, m/z 437 ($M+H^+$).

Example 30: 3-[3,5-dimethyl-4-(3-trifluoromethyl-benzyl)-pyrazol-1-yl]-5-methyl-5*H*-1,2,4-triazino[5,6-*b*]indole

In a manner analogous to Example 5, using Intermediate 2 (9.4 mg, 44 µmol) and Intermediate 15 (34 mg, 132 µmol), was prepared the title compound (9 mg, 47%). Hplc/ms (positive ion) Rt 4.75 min, m/z 437 ($M+H^+$).

Example 31: 3-[3,5-dimethyl-4-(2-methyl-benzyl)-pyrazol-1-yl]-5-methyl-5*H*-1,2,4-triazino[5,6-*b*]indole

In a manner analogous to Example 5, using Intermediate 2 (9.4 mg, 44 µmol) and Intermediate 25 (27 mg, 132 µmol), was prepared the title compound (5 mg, 30%). Hplc/ms (positive ion) Rt 4.64 min, m/z 383 ($M+H^+$).

Example 32: 3-[3,5-dimethyl-4-(3-methyl-benzyl)-pyrazol-1-yl]-5-methyl-5*H*-1,2,4-triazino[5,6-*b*]indole

In a manner analogous to Example 5, using Intermediate 2 (9.4 mg, 44 µmol) and Intermediate 26 (27 mg, 132 µmol), was prepared the title compound (7 mg, 42%). Hplc/ms (positive ion) Rt 4.68 min, m/z 383 ($M+H^+$).

Example 33: 3-(3,5-dimethyl-4-phenethyl-pyrazol-1-yl)-5-methyl-5*H*-1,2,4-triazino[5,6-*b*]indole

In a manner analogous to Example 5, using Intermediate 2 (9.4 mg, 44 µmol) and Intermediate 27 (27 mg, 132 µmol), was prepared the title compound (10 mg, 59%). Hplc/ms (positive ion) Rt 4.69 min, m/z 383 ($M+H^+$).

Example 34: 4-[3,5-dimethyl-1-(5-methyl-5*H*-1,2,4-triazino[5,6-*b*]indol-3-yl)-1*H*-pyrazol-4-ylmethyl]-benzoic acid methyl ester

In a manner analogous to Example 5, using Intermediate 2 (47 mg, 440 µmol) and Intermediate 28 (165 mg, 660 µmol), was prepared the title compound (67 mg, 36%). Hplc/ms (positive ion) Rt 4.28 min, m/z 427 ($M+H^+$).

Example 35: 3-[3,5-dimethyl-1-(5-methyl-5*H*-1,2,4-triazino[5,6-*b*]indol-3-yl)-1*H*-pyrazol-4-ylmethyl]-benzoic acid methyl ester

In a manner analogous to Example 5, using Intermediate 2 (47 mg, 440 µmol) and Intermediate 29 (165 mg, 660 µmol), was prepared the title compound (66 mg, 36%). Hplc/ms (positive ion) Rt 4.28 min, m/z 427 ($M+H^+$).

Example 36: acetic acid 4-[3,5-dimethyl-1-(5-methyl-5*H*-1,2,4-triazino[5,6-*b*]indol-3-yl)-1*H*-pyrazol-4-ylmethyl]-phenyl ester

A mixture of 4-[3,5-dimethyl-1-(5-methyl-5*H*-1,2,4-triazino[5,6-*b*]indol-3-yl)-1*H*-pyrazol-4-ylmethyl]-phenol (Example 25, 10 mg, 26µmol) and pyridine (10 µL, 124 µmol) in dry acetonitrile (1 ml) was treated with acetyl chloride (10 µL, 140 µmol) and heated to 150°C in a sealed vial under microwave conditions for 2 minutes. The mixture was cooled to room temperature and treated with water (1 ml). The suspension was filtered and the solid washed with water (1 ml), hexane (1 ml) and dried in vacuo to give the title compound (2.07 mg, 18%). Hplc/ms (positive ion) Rt 4.18 min, m/z 427 ($M+H^+$).

Example 37: acetic acid 3-[3,5-dimethyl-1-(5-methyl-5*H*-1,2,4-triazino[5,6-*b*]indol-3-yl)-1*H*-pyrazol-4-ylmethyl]-phenyl ester

In a manner analogous to that of Example 36, using 3-[3,5-dimethyl-1-(5-methyl-5*H*-1,2,4-triazino[5,6-*b*]indol-3-yl)-1*H*-pyrazol-4-ylmethyl]-phenol (Example 26, 10 mg, 26µmol) was prepared the title compound (5.67 mg, 51%). Hplc/ms (positive ion) Rt 4.19 min, m/z 427 ($M+H^+$).

Example 38: acetic acid 2-[3,5-dimethyl-1-(5-methyl-5*H*-1,2,4-triazino[5,6-*b*]indol-3-yl)-1*H*-pyrazol-4-ylmethyl]-phenyl ester

In a manner analogous to that of Example 36, using 2-[3,5-dimethyl-1-(5-methyl-5*H*-1,2,4-triazino[5,6-*b*]indol-3-yl)-1*H*-pyrazol-4-ylmethyl]-phenol (Example 20, 10 mg, 26µmol) was prepared the title compound (2 mg, 18%). Hplc/ms (positive ion) Rt 4.18 min, m/z 427 ($M+H^+$).

Example 39: 5-ethyl-3-[4-(2-methoxy-benzyl)-3,5-dimethyl-pyrazol-1-yl]-5*H*-1,2,4-triazino[5,6-*b*]indole

In a manner analogous to Example 14, using (5-ethyl-5*H*-1,2,4-triazino[5,6-*b*]indol-3-yl)-hydrazine (Intermediate 31, 10 mg, 44 µmol) was prepared the title compound (8 mg, 44%). Hplc/ms (positive ion) Rt 4.56 min, m/z 413 ($M+H^+$).

Example 40: 5-ethyl-3-[4-(2-fluoro-benzyl)-3,5-dimethyl-pyrazol-1-yl]-5*H*-1,2,4-triazino[5,6-*b*]indole

In a manner analogous to Example 12, using (5-ethyl-5*H*-1,2,4-triazino[5,6-*b*]indol-3-yl)-hydrazine (Intermediate 31, 10 mg, 44 µmol) in place of Intermediate 4, was prepared the title compound (5 mg, 28%). Hplc/ms (positive ion) Rt 4.67 min, m/z 401 ($M+H^+$).

Example 41: 5-ethyl-3-[4-(3-fluoro-benzyl)-3,5-dimethyl-pyrazol-1-yl]-5*H*-1,2,4-triazino[5,6-*b*]indole

In a manner analogous to Example 15, using (5-ethyl-5*H*-1,2,4-triazino[5,6-*b*]indol-3-yl)-hydrazine (Intermediate 31, 10 mg, 44 µmol) in place of Intermediate 2, was prepared the title compound (4 mg, 23%). Hplc/ms (positive ion) Rt 4.64 min, m/z 401 ($M+H^+$).

Example 42: 5-ethyl-3-[4-(4-fluoro-benzyl)-3,5-dimethyl-pyrazol-1-yl]-5*H*-1,2,4-triazino[5,6-*b*]indole

In a manner analogous to Example 15, using (5-ethyl-5*H*-1,2,4-triazino[5,6-*b*]indol-3-yl)-hydrazine (Intermediate 31, 10 mg, 44 µmol) in place of Intermediate 2 and Intermediate 32 in place of Intermediate 17, was prepared the title compound (7 mg, 40%). Hplc/ms (positive ion) Rt 4.64 min, m/z 401 ($M+H^+$).

Example 43: 5-ethyl-3-[4-(3-methoxy-benzyl)-3,5-dimethyl-pyrazol-1-yl]-5*H*-1,2,4-triazino[5,6-*b*]indole

In a manner analogous to Example 16, using (5-ethyl-5*H*-1,2,4-triazino[5,6-*b*]indol-3-yl)-hydrazine (Intermediate 31, 10 mg, 44 µmol) in place of Intermediate 2, was prepared the title compound (5 mg, 28%). Hplc/ms (positive ion) Rt 4.55 min, m/z 413 ($M+H^+$).

Example 44: 3-[4-(3,5-dimethoxy-benzyl)-3,5-dimethyl-pyrazol-1-yl]-5-ethyl-5*H*-1,2,4-triazino[5,6-*b*]indole

In a manner analogous to Example 17, using (5-ethyl-5*H*-1,2,4-triazino[5,6-*b*]indol-3-yl)-hydrazine (Intermediate 31, 10 mg, 44 µmol) in place of Intermediate 2, was prepared the title compound (5 mg, 26%). Hplc/ms (positive ion) Rt 4.52 min, m/z 443 ($M+H^+$).

Example 45: 3-[3,5-dimethyl-4-(2-nitro-benzyl)-pyrazol-1-yl]-5-ethyl-5*H*-1,2,4-triazino[5,6-*b*]indole

In a manner analogous to Example 18, using (5-ethyl-5*H*-1,2,4-triazino[5,6-*b*]indol-3-yl)-hydrazine (Intermediate 31, 10 mg, 44 µmol) in place of Intermediate 2, was prepared the title compound (10 mg, 53%). Hplc/ms (positive ion) Rt 4.47 min, m/z 428 ($M+H^+$).

Example 46: 2-[1-(5-ethyl-5*H*-1,2,4-triazino[5,6-*b*]indol-3-yl)-3,5-dimethyl-1*H*-pyrazol-4-ylmethyl]-phenol

In a manner analogous to Example 8, using (5-ethyl-5*H*-1,2,4-triazino[5,6-*b*]indol-3-yl)-hydrazine (Intermediate 31, 10 mg, 44 µmol) in place of Intermediate 4, was prepared the title compound (1.5 mg, 9%). Hplc/ms (positive ion) Rt 4.03 min, m/z 399 ($M+H^+$).

Example 47: 5-ethyl-3-[4-(4-methoxy-benzyl)-3,5-dimethyl-pyrazol-1-yl]-5*H*-1,2,4-triazino[5,6-*b*]indole

In a manner analogous to Example 20, using (5-ethyl-5*H*-1,2,4-triazino[5,6-*b*]indol-3-yl)-hydrazine (Intermediate 31, 10 mg, 44 µmol) in place of Intermediate 2, was prepared the title compound (5 mg, 28%). Hplc/ms (positive ion) Rt 4.54 min, m/z 413 ($M+H^+$).

Example 48: 3-[4-(2-benzyloxy-benzyl)-3,5-dimethyl-pyrazol-1-yl]-5-ethyl-5*H*-1,2,4-triazino[5,6-*b*]indole

In a manner analogous to Example 6, using (5-ethyl-5*H*-1,2,4-triazino[5,6-*b*]indol-3-yl)-hydrazine (Intermediate 31, 10 mg, 44 µmol) in place of Intermediate 4, was prepared the title compound (7 mg, 33%). Hplc/ms (positive ion) Rt 5.19 min, m/z 489 ($M+H^+$).

Example 49: 3-(3,5-dimethyl-4-naphthalen-2-ylmethyl-pyrazol-1-yl)-5-ethyl-5*H*-1,2,4-triazino[5,6-*b*]indole

In a manner analogous to Example 11, using (5-ethyl-5*H*-1,2,4-triazino[5,6-*b*]indol-3-yl)-hydrazine (Intermediate 31, 10 mg, 44 µmol) in place of Intermediate 4, was prepared the title compound (3.3 mg, 17%). Hplc/ms (positive ion) Rt 5.04 min, m/z 433 ($M+H^+$).

Example 50: 3-[3,5-dimethyl-4-(3-nitro-benzyl)-pyrazol-1-yl]-5-ethyl-5*H*-1,2,4-triazino[5,6-*b*]indole

In a manner analogous to Example 5, using (5-ethyl-5*H*-1,2,4-triazino[5,6-*b*]indol-3-yl)-hydrazine (Intermediate 31, 10 mg, 44 µmol) and 3-(3-nitro-benzyl)-pentane-2,4-dione (Intermediate 33, 52 mg, 220 µmol), was prepared the title compound (3.4 mg, 18%). Hplc/ms (positive ion) Rt 4.5 min, m/z 428 ($M+H^+$).

Example 51: 3-[3,5-dimethyl-4-(4-nitro-benzyl)-pyrazol-1-yl]-5-ethyl-5*H*-1,2,4-triazino[5,6-*b*]indole

In a manner analogous to Example 24, using (5-ethyl-5*H*-1,2,4-triazino[5,6-*b*]indol-3-yl)-hydrazine (Intermediate 31, 10 mg, 44 µmol) in place of Intermediate 2, was prepared the title compound (4.5 mg, 24%). Hplc/ms (positive ion) Rt 4.51 min, m/z 428 ($M+H^+$).

Example 52: 4-[1-(5-ethyl-5*H*-1,2,4-triazino[5,6-*b*]indol-3-yl)-3,5-dimethyl-1*H*-pyrazol-4-ylmethyl]-phenol

In a manner analogous to Example 7, using (5-ethyl-5*H*-1,2,4-triazino[5,6-*b*]indol-3-yl)-hydrazine (Intermediate 31, 10 mg, 44 µmol) in place of Intermediate 4, was prepared the title compound (13 mg, 74%). Hplc/ms (positive ion) Rt 3.92 min, m/z 399 ($M+H^+$).

Example 53: 3-[1-(5-ethyl-5*H*-1,2,4-triazino[5,6-*b*]indol-3-yl)-3,5-dimethyl-1*H*-pyrazol-4-ylmethyl]-phenol

In a manner analogous to Example 9, using (5-ethyl-5*H*-1,2,4-triazino[5,6-*b*]indol-3-yl)-hydrazine (Intermediate 31, 10 mg, 44 µmol) in place of Intermediate 4, was prepared the title compound (9 mg, 51%). Hplc/ms (positive ion) Rt 3.99 min, m/z 399 ($M+H^+$).

Example 54: 3-[3,5-dimethyl-4-(4-trifluoromethyl-benzyl)-pyrazol-1-yl]-5-ethyl-5*H*-1,2,4-triazino[5,6-*b*]indole

In a manner analogous to Example 27, using (5-ethyl-5*H*-1,2,4-triazino[5,6-*b*]indol-3-yl)-hydrazine (Intermediate 31, 10 mg, 44 µmol) in place of Intermediate 2, was prepared the title compound (10 mg, 50%). Hplc/ms (positive ion) Rt 4.97 min, m/z 451 ($M+H^+$).

Example 55: 5-ethyl-3-[4-(4-methanesulphonyl-benzyl)-3,5-dimethyl-pyrazol-1-yl]-5*H*-1,2,4-triazino[5,6-*b*]indole

In a manner analogous to Example 28, using (5-ethyl-5*H*-1,2,4-triazino[5,6-*b*]indol-3-yl)-hydrazine (Intermediate 31, 10 mg, 44 µmol) in place of Intermediate 2, was prepared the title compound (1 mg, 5%). Hplc/ms (positive ion) Rt 3.92 min, m/z 461 ($M+H^+$).

Example 56: 3-[3,5-dimethyl-4-(2-trifluoromethyl-benzyl)-pyrazol-1-yl]-5-ethyl-5*H*-1,2,4-triazino[5,6-*b*]indole

In a manner analogous to Example 29, using (5-ethyl-5*H*-1,2,4-triazino[5,6-*b*]indol-3-yl)-hydrazine (Intermediate 31, 10 mg, 44 µmol) in place of Intermediate 2, was prepared the title compound (2 mg, 10%). Hplc/ms (positive ion) Rt 5.06 min, m/z 451 ($M+H^+$).

Example 57: 3-[3,5-dimethyl-4-(3-trifluoromethyl-benzyl)-pyrazol-1-yl]-5-ethyl-5*H*-1,2,4-triazino[5,6-*b*]indole

In a manner analogous to Example 30, using (5-ethyl-5*H*-1,2,4-triazino[5,6-*b*]indol-3-yl)-hydrazine (Intermediate 31, 10 mg, 44 µmol) in place of Intermediate 2, was prepared the title compound (8 mg, 40%). Hplc/ms (positive ion) Rt 4.94 min, m/z 451 ($M+H^+$).

Example 58: 3-[3,5-dimethyl-4-(2-methyl-benzyl)-pyrazol-1-yl]-5-ethyl-5*H*-1,2,4-triazino[5,6-*b*]indole

In a manner analogous to Example 31, using (5-ethyl-5*H*-1,2,4-triazino[5,6-*b*]indol-3-yl)-hydrazine (Intermediate 31, 10 mg, 44 µmol) in place of Intermediate 2, was prepared the title compound (8 mg, 46%). Hplc/ms (positive ion) Rt 4.85 min, m/z 397 ($M+H^+$).

Example 59: 3-[3,5-dimethyl-4-(3-methyl-benzyl)-pyrazol-1-yl]-5-ethyl-5*H*-1,2,4-triazino[5,6-*b*]indole

In a manner analogous to Example 32, using (5-ethyl-5*H*-1,2,4-triazino[5,6-*b*]indol-3-yl)-hydrazine (Intermediate 31, 10 mg, 44 µmol) in place of Intermediate 2, was prepared the title compound (9 mg, 52%). Hplc/ms (positive ion) Rt 4.86 min, m/z 397 ($M+H^+$).

Example 60: 3-(3,5-dimethyl-4-phenethyl-pyrazol-1-yl)-5-ethyl-5*H*-1,2,4-triazino[5,6-*b*]indole

In a manner analogous to Example 33, using (5-ethyl-5*H*-1,2,4-triazino[5,6-*b*]indol-3-yl)-hydrazine (Intermediate 31, 10 mg, 44 µmol) in place of Intermediate 2, was prepared the title compound (7 mg, 40%). Hplc/ms (positive ion) Rt 4.89 min, m/z 397 ($M+H^+$).

Example 61: 4-[1-(5-ethyl-5*H*-1,2,4-triazino[5,6-*b*]indol-3-yl)-3,5-dimethyl-1*H*-pyrazol-4-ylmethyl]-benzoic acid methyl ester

In a manner analogous to Example 34, using (5-ethyl-5*H*-1,2,4-triazino[5,6-*b*]indol-3-yl)-hydrazine (Intermediate 31, 50 mg, 220 µmol) in place of Intermediate 2, was prepared the title compound (73 mg, 75%). Hplc/ms (positive ion) Rt 4.49 min, m/z 441 ($M+H^+$).

Example 62: 3-[1-(5-ethyl-5*H*-1,2,4-triazino[5,6-*b*]indol-3-yl)-3,5-dimethyl-1*H*-pyrazol-4-ylmethyl]-benzoic acid methyl ester

In a manner analogous to Example 35, using (5-ethyl-5*H*-1,2,4-triazino[5,6-*b*]indol-3-yl)-hydrazine (Intermediate 31, 50 mg, 220 µmol) in place of Intermediate 2, was prepared the title compound (50 mg, 52%). Hplc/ms (positive ion) Rt 4.49 min, m/z 441 ($M+H^+$).

Example 63: 4-[1-(5-ethyl-5*H*-1,2,4-triazino[5,6-*b*]indol-3-yl)-3,5-dimethyl-1*H*-pyrazol-4-ylmethyl]-benzoic acid

A stirred solution of 4-[1-(5-ethyl-5*H*-1,2,4-triazino[5,6-*b*]indol-3-yl)-3,5-dimethyl-1*H*-pyrazol-4-ylmethyl]-benzoic acid methyl ester (Example 61, 22 mg, 50 µmol) 3:1 tetrahydrofuran/water (2 ml) was treated with lithium hydroxide (12 mg, 500 µmol) and stirred at room temperature for 17 hours. Solvent was evaporated and the residue dissolved in water, acidified with 1M hydrochloric acid, and extracted with dichloromethane (3 x 5 ml). The combined extracts were dried over magnesium sulphate, filtered and evaporated to give the title compound (15 mg, 70%). Hplc/ms (positive ion) Rt 3.86 min, m/z 427 ($M+H^+$).

Example 64: 3-(3,5-dimethyl-4-propyl-pyrazol-1-yl)-5-ethyl-5*H*-1,2,4-triazino[5,6-*b*]indole

A solution of (5*H*-1,2,4-triazino[5,6-*b*]indol-3-yl)-hydrazine (Intermediate 4 , 300 mg, 1.5 mmol) in 20% acetic acid/ethanol (4 ml) was treated with 3-propyl-pentane-2,4-dione (1.065 g, 7.5 mmol) and heated to 140°C in a sealed vial under microwave conditions for 5 minutes. On cooling, the resulting precipitate was filtered and dried under vacuum to give 3-(3,5-dimethyl-4-propyl-pyrazol-1-yl)-5*H*-1,2,4-triazino[5,6-*b*]indole (315 mg, 70%) as a pale yellow solid.

A solution of the product (40 mg, 130 µmol) in acetone (2ml) was treated with potassium carbonate (37 mg, 260 µmol) and ethyl iodide (22 mg, 140 µmol) then heated to 100°C in a sealed vial under microwave conditions for 8 minutes. Solvent was evaporated and the residue purified by preparative hplc to give the title compound (15 mg, 35%). Hplc/ms (positive ion) Rt 4.57 min, m/z 335 ($M+H^+$).

Example 65: 5-ethyl-3-(4-ethyl-3,5-dimethyl-pyrazol-1-yl)-5*H*-1,2,4-triazino[5,6-*b*]indole

In a manner analogous to Example 64, using 3-(4-ethyl-3,5-dimethyl-pyrazol-1-yl)-5*H*-1,2,4-triazino[5,6-*b*]indole (Example 4, 50 mg, 170 µmol), was prepared the title compound (10 mg, 18%). Hplc/ms (positive ion) Rt 4.3 min, m/z 321 ($M+H^+$).

Example 66: 3-(4-benzyl-3,5-dimethyl-pyrazol-1-yl)-5-propyl-5*H*-1,2,4-triazino[5,6-*b*]indole

In a manner analogous to Example 64, using 3-(4-benzyl-3,5-dimethyl-pyrazol-1-yl)-5*H*-1,2,4-triazino[5,6-*b*]indole (Example 5, 30 mg, 85 µmol) and 1-iodopropane (16 mg, 94 µmol), was prepared the title compound (5 mg, 15%). Hplc/ms (positive ion) Rt 4.85 min, m/z 397 ($M+H^+$).

Example 67: 5-propyl-3-(3,4,5-trimethyl-pyrazol-1-yl)-5*H*-1,2,4-triazino[5,6-*b*]indole

A solution of (5*H*-1,2,4-triazino[5,6-*b*]indol-3-yl)-hydrazine (Intermediate 4 , 300 mg, 1.5 mmol) in 20% acetic acid/ethanol (4 ml) was treated with 3-methyl-pentane-2,4-dione (855 mg, 7.5 mmol) and heated to 140°C in a sealed vial under microwave conditions for 5 minutes. On cooling, the resulting precipitate was filtered and dried under vacuum to give 3-(3,4,5-trimethyl-pyrazol-1-yl)-5*H*-1,2,4-triazino[5,6-*b*]indole (330 mg, 80%) as a pale yellow solid. The product (50 mg, 180 µmol) in acetone (2 ml) was treated with potassium carbonate (50 mg, 360 µmol), 1-iodopropane (34 mg, 200 µmol) and heated to 100°C in a sealed vial under microwave conditions for 8 minutes. Solvent was evaporated and the residue purified by preparative hplc to give the title compound (10 mg, 17%). Hplc/ms (positive ion) Rt 4.28 min, m/z 321 ($M+H^+$).

Example 68: 3-(4-ethyl-3,5-dimethyl-pyrazol-1-yl)-5-propyl-5*H*-1,2,4-triazino[5,6-*b*]indole

In a manner analogous to Example 64, using 3-(4-ethyl-3,5-dimethyl-pyrazol-1-yl)-5*H*-1,2,4-triazino[5,6-*b*]indole (Example 4, 50 mg, 170 µmol) and 1-iodopropane (32 mg, 190 µmol), was prepared the title compound (15 mg, 26%). Hplc/ms (positive ion) Rt 4.53 min, m/z 335 ($M+H^+$).

Example 69: 3-(3,5-dimethyl-4-propyl-pyrazol-1-yl)-5-propyl-5*H*-1,2,4-triazino[5,6-*b*]indole

In a manner analogous to Example 64, using 1-iodopropane (44 mg, 260 µmol), was prepared the title compound (15 mg, 33%). Hplc/ms (positive ion) Rt 4.8 min, m/z 349 ($M+H^+$).

Example 70: 5-butyl-3-(3,5-dimethyl-pyrazol-1-yl)-5*H*-1,2,4-triazino[5,6-*b*]indole

A mixture of (5*H*-1,2,4-triazino[5,6-*b*]indol-3-yl)-hydrazine (300 mg, 1.5 mmol) and pentane-2,4-dione (750 mg, 7.5 mmol) in 20% acetic acid/ethanol (4 ml) was heated to 140°C in a sealed vial under microwave conditions for 5 minutes. The reaction mixture was cooled to room temperature and the suspension filtered to give 3-(3,5-dimethyl-pyrazol-1-yl)-5*H*-1,2,4-triazino[5,6-*b*]indole (360 mg, 91%) as a pale yellow solid. The product (50 mg, 190µmol) in acetone (2 ml) was treated with potassium carbonate (54 mg, 380 µmol) and 1-bromobutane (29 mg, 210 µmol). The mixture was heated to 100°C in a sealed vial under microwave conditions for 8 minutes. The reaction mixture was cooled to room temperature, filtered and the filtrate evaporated. The residue was triturated with diethyl ether, filtered and dried to give the title compound (5 mg, 8%). Hplc/ms (positive ion) Rt 4.38 min, m/z 321 ($M+H^+$).

Example 71: 5-butyl-3-(3,4,5-trimethyl-pyrazol-1-yl)-5*H*-1,2,4-triazino[5,6-*b*]indole

In a manner analogous to Example 70, using 3-methyl pentane-2,4-dione in place of pentane-2,4-dione, was prepared the title compound (7 mg, 12%). Hplc/ms (positive ion) Rt 4.58 min, m/z 335 ($M+H^+$).

Example 72: 3-(4-benzyl-3,5-dimethyl-pyrazol-1-yl)-5-butyl-5*H*-1,2,4-triazino[5,6-*b*]indole

In a manner analogous to Example 66, using 1-bromobutane (13 mg, 94 µmol), was prepared the title compound (5 mg, 14%). Hplc/ms (positive ion) Rt 5.1 min, m/z 411 ($M+H^+$).

Example 73: 5-butyl-3-(3,5-dimethyl-4-naphthalen-2-ylmethyl-pyrazol-1-yl)-5*H*-1,2,4-triazino[5,6-*b*]indole

In a manner analogous to Example 64, using 3-(3,5-dimethyl-4-naphthalen-2-ylmethyl-pyrazol-1-yl)-5*H*-1,2,4-triazino[5,6-*b*]indole (Example 11, 30 mg, 74 µmol) and 1-bromobutane (11 mg, 80 µmol), was prepared the title compound (5 mg, 15%). Hplc/ms (positive ion) Rt 5.47 min, m/z 461 ($M+H^+$).

Example 74: 5-butyl-3-[4-(2-fluoro-benzyl)-3,5-dimethyl-pyrazol-1-yl]-5*H*-1,2,4-triazino[5,6-*b*]indole

In a manner analogous to Example 64, using 3-[4-(2-fluoro-benzyl)-3,5-dimethyl-pyrazol-1-yl]-5*H*-1,2,4-triazino[5,6-*b*]indole (Example 12, 30 mg, 74 µmol) and 1-bromobutane (11 mg, 80 µmol), was prepared the title compound (5 mg, 16%). Hplc/ms (positive ion) Rt 5.12 min, m/z 429 ($M+H^+$).

Example 75: 5-butyl-3-[3,5-dimethyl-4-(3-trifluoromethyl-benzyl)-pyrazol-1-yl]-5*H*-1,2,4-triazino[5,6-*b*]indole

In a manner analogous to Example 64, using 3-[3,5-dimethyl-4-(3-trifluoromethyl-benzyl)-pyrazol-1-yl]-5*H*-1,2,4-triazino[5,6-*b*]indole (Example 13, 30 mg, 71 µmol) and 1-bromobutane (11 mg, 80 µmol), was prepared the title compound (5 mg, 15%). Hplc/ms (positive ion) Rt 5.34 min, m/z 479 ($M+H^+$).

Example 76: 5-butyl-3-(4-ethyl-3,5-dimethyl-pyrazol-1-yl)-5*H*-1,2,4-triazino[5,6-*b*]indole

In a manner analogous to Example 64, using 3-(4-ethyl-3,5-dimethyl-pyrazol-1-yl)-5*H*-1,2,4-triazino[5,6-*b*]indole (Example 4, 50 mg, 170 µmol) and 1-bromobutane (26 mg, 190 µmol), was prepared the title compound (15 mg, 25%). Hplc/ms (positive ion) Rt 4.8 min, m/z 349 ($M+H^+$).

Example 77: 5-benzyl-3-(3,4,5-trimethyl-pyrazol-1-yl)-5*H*-1,2,4-triazino[5,6-*b*]indole

In a manner analogous to Example 67, using benzyl bromide (34 mg, 200 µmol) in place of 1-iodopropane, was prepared the title compound (30 mg, 45%). Hplc/ms (positive ion) Rt 4.49 min, m/z 369 ($M+H^+$).

Example 78: 3-(4-benzyl-3,5-dimethyl-pyrazol-1-yl)-5-isobutyl-5*H*-1,2,4-triazino[5,6-*b*]indole

In a manner analogous to Example 64, using 3-(4-benzyl-3,5-dimethyl-pyrazol-1-yl)-5*H*-1,2,4-triazino[5,6-*b*]indole (Example 5, 50 mg, 140 µmol) and

1-iodo-2-methylpropane (28 mg, 150 µmol), was prepared the title compound (25 mg, 44%). Hplc/ms (positive ion) Rt 5.05 min, m/z 411 ($M+H^+$).

Example 79: 5-benzyl-3-(3,5-dimethyl-4-propyl-pyrazol-1-yl)-5*H*-1,2,4-triazino[5,6-*b*]indole

In a manner analogous to Example 64, using benzyl bromide (24 mg, 140 µmol), was prepared the title compound (20 mg, 39%). Hplc/ms (positive ion) Rt 4.94 min, m/z 397 ($M+H^+$).

Example 80: oxalic acid 4-[3,5-dimethyl-1-(5-methyl-5*H*-1,2,4-triazino[5,6-*b*]indol-3-yl)-1*H*-pyrazol-4-ylmethyl]-phenyl ester ethyl ester

In a manner analogous to Example 36, using ethyl chlorooxalate (10 µL, 90 µmol) in place of acetyl chloride, was prepared the title compound (8.9 mg, 71%). Hplc/ms (positive ion) Rt 4.31 min, m/z 485 ($M+H^+$).

Example 81: 5-isobutyl-3-(3,4,5-trimethyl-pyrazol-1-yl)-5*H*-1,2,4-triazino[5,6-*b*]indole

In a manner analogous to Example 67, using 3-(3,4,5-trimethyl-pyrazol-1-yl)-5*H*-1,2,4-triazino[5,6-*b*]indole (80 mg, 290 µmol) and 1-iodo-2-methylpropane (59 mg, 320 µmol), was prepared the title compound (10 mg, 10%). Hplc/ms (positive ion) Rt 4.53 min, m/z 335 ($M+H^+$).

Example 82: 3-(4-ethyl-3,5-dimethyl-pyrazol-1-yl)-5-isobutyl-5*H*-1,2,4-triazino[5,6-*b*]indole

In a manner analogous to Example 64, using 3-(4-ethyl-3,5-dimethyl-pyrazol-1-yl)-5*H*-1,2,4-triazino[5,6-*b*]indole (Example 4, 50 mg, 170 µmol) and 1-iodo-2-methylpropane (35 mg, 190 µmol), was prepared the title compound (10 mg, 17%). Hplc/ms (positive ion) Rt 4.76 min, m/z 349 ($M+H^+$).

Example 83: 3-(3,5-dimethyl-4-propyl-pyrazol-1-yl)-5-isobutyl-5*H*-1,2,4-triazino[5,6-*b*]indole

In a manner analogous to Example 64, using 1-iodo-2-methylpropane (26 mg, 140 µmol), was prepared the title compound (5 mg, 11%). Hplc/ms (positive ion) Rt 5.01 min, m/z 363 ($M+H^+$).

Example 84: 3-(3,5-dimethyl-4-propyl-pyrazol-1-yl)-5-isobutyl-5*H*-1,2,4-triazino[5,6-*b*]indole

A mixture of 3-(3,5-dimethyl-4-propyl-pyrazol-1-yl)-5*H*-1,2,4-triazino[5,6-*b*]indole (30 mg, 100 µmol, prepared as in Example 64), potassium carbonate (42 mg, 300 µmol) and 1-(2-chloroethyl)-pyrrolidine hydrochloride (19 mg, 110 µmol) in acetone (2 ml) was heated to 100°C in a sealed vial under microwave conditions for 8 minutes. After cooling to room temperature, solvent was evaporated and the residue subjected to preparative HPLC to give the title compound (15mg, 37%). Hplc/ms (positive ion) Rt 3.2 min, m/z 404 ($M+H^+$).

Example 85: 2-[3-(3,5-dimethyl-4-propyl-pyrazol-1-yl)-1,2,4-triazino[5,6-*b*]indol-5-yl]-ethanol

A solution of 3-(3,5-dimethyl-4-propyl-pyrazol-1-yl)-5-[2-(tetrahydro-pyran-2-yloxy)-ethyl]-5*H*-1,2,4-triazino[5,6-*b*]indole (Example 95, 10 mg, 23 µmol) in 4:2:1 acetic acid:tetrahydrofuran:water (1 ml) was heated to 100°C in a sealed vial under microwave conditions for 10 minutes. After cooling to room temperature, solvent was evaporated and the residue subjected to preparative HPLC to give the title compound (5 mg, 62%). Hplc/ms (positive ion) Rt 3.89 min, m/z 351 ($M+H^+$).

Example 86: 3-[3,5-dimethyl-4-(1-phenyl-ethyl)-pyrazol-1-yl]-5-methyl-5*H*-1,2,4-triazino[5,6-*b*]indole

In a manner analogous to Example 2, using 3-(1-phenyl-ethyl)-pentane-2,4-dione (Intermediate 34, 45 mg, 219 µmol) in place of 3-propyl-2,4-pentanedione, was prepared the title compound (13 mg, 77%). Hplc/ms (positive ion) Rt 4.62 min, m/z 383 ($M+H^+$).

Example 87: 3-(4-benzhydryl-3,5-dimethyl-pyrazol-1-yl)-5-methyl-5*H*-1,2,4-triazino[5,6-*b*]indole

In a manner analogous to Example 2, using 3-benzhydryl-pentane-2,4-dione (Intermediate 35, 55 mg, 219 µmol) in place of 3-propyl-2,4-pentanedione, was prepared the title compound (7 mg, 36%). Hplc/ms (positive ion) Rt 4.99 min, m/z 445 ($M+H^+$).

Example 88: 3-[3,5-dimethyl-4-(1-phenyl-ethyl)-pyrazol-1-yl]-5-ethyl-5*H*-1,2,4-triazino[5,6-*b*]indole

In a manner analogous to Example 86, using (5-ethyl-5*H*-1,2,4-

triazino[5,6-*b*]indol-3-yl)-hydrazine (Intermediate 31, 10 mg, 44 µmol), was prepared the title compound (3 mg, 17%). Hplc/ms (positive ion) Rt 4.83 min, m/z 397 ($M+H^+$).

Example 89: 3-(4-benzhydryl-3,5-dimethyl-pyrazol-1-yl)-5-ethyl-5*H*-1,2,4-triazino[5,6-*b*]indole

In a manner analogous to Example 87, using (5-ethyl-5*H*-1,2,4-triazino[5,6-*b*]indol-3-yl)-hydrazine (Intermediate 31, 10 mg, 44 µmol), was prepared the title compound (1.6 mg, 8%). Hplc/ms (positive ion) Rt 5.18 min, m/z 459 ($M+H^+$).

Example 90: 3-[4-(4-methoxy-phenyl)-pyrazol-1-yl]-5-methyl-5*H*-1,2,4-triazino[5,6-*b*]indole

A solution of (5-methyl-5*H*-1,2,4-triazino[5,6-*b*]indol-3-yl)-hydrazine (Intermediate 2, 9.4 mg, 44 µmol) and 2-(4-methoxy-phenyl)-malonaldehyde (24 mg, 135 µmol) in 4:1 ethanol:acetic acid (1 ml) was heated at 140°C in a sealed vial under microwave conditions for 5 minutes. After cooling to room temperature, the mixture was treated with water (1 ml) and the precipitate filtered. The solid was washed with water (1 ml), hexane (2 ml) and dried in vacuo to give the title compound (10 mg, 64%). Hplc/ms (positive ion) Rt 4.16 min, m/z 357 ($M+H^+$).

Example 91: 3-[4-(3-bromo-phenyl)-pyrazol-1-yl]-5-methyl-5*H*-1,2,4-triazino[5,6-*b*]indole

In a manner analogous to Example 90, using 2-(3-bromophenyl)-malonaldehyde (30 mg, 132 µmol), was prepared the title compound (8 mg, 45%). Hplc/ms (positive ion) Rt 4.63 min, m/z 405 ($M+H^+$).

Example 92: 5-methyl-3-(4-quinolin-4-yl-pyrazol-1-yl)-5*H*-1,2,4-triazino[5,6-*b*]indole

In a manner analogous to Example 90, using 2-quinolin-4-yl-malonaldehyde (26 mg, 130 µmol), was prepared the title compound (8 mg, 48%). Hplc/ms (positive ion) Rt 3.5 min, m/z 378 ($M+H^+$).

Example 93: 5-methyl-3-(4-pyridin-2-yl-pyrazol-1-yl)-5*H*-1,2,4-triazino[5,6-*b*]indole

In a manner analogous to Example 90, using 2-pyridin-2-yl-malonaldehyde (20 mg, 134 µmol), was prepared the title compound (2.5 mg, 17%). Hplc/ms (positive ion) Rt 3.35 min, m/z 328 ($M+H^+$).

Example 94: 3-[4-(4-bromo-phenyl)-pyrazol-1-yl]-5-methyl-5*H*-1,2,4-triazino[5,6-*b*]indole

In a manner analogous to Example 90, using 2-(4-bromophenyl)-malonaldehyde (30 mg, 132 µmol), was prepared the title compound (7 mg, 39%). Hplc/ms (positive ion) Rt 4.65 min, m/z 405 ($M+H^+$).

Example 95: 3-(3,5-dimethyl-4-propyl-pyrazol-1-yl)-5-[2-(tetrahydro-pyran-2-yloxy)-ethyl]-5*H*-1,2,4-triazino[5,6-*b*]indole

In a manner analogous to Example 64, using 3-(3,5-dimethyl-4-propyl-pyrazol-1-yl)-5*H*-1,2,4-triazino[5,6-*b*]indole (50 mg, 163 µmol) and 2-(2-bromoethoxy)-tetrahydropyran (37 mg, 180 µmol), was prepared the title compound (70 mg, 100%). Hplc/ms (positive ion) Rt 4.79 min, m/z 435 ($M+H^+$).

Example 96: 5-[2-(tetrahydro-pyran-2-yloxy)-ethyl]-3-(3,4,5-trimethyl-pyrazol-1-yl)-5*H*-1,2,4-triazino[5,6-*b*]indole

In a manner analogous to Example 67, using 2-(2-bromoethoxy)-tetrahydropyran (41 mg, 198 µmol), was prepared the title compound (20 mg, 27%). Hplc/ms (positive ion) Rt 4.29 min, m/z 407 ($M+H^+$).

Example 97: 3-(4-benzyl-3,5-dimethyl-pyrazol-1-yl)-5-[2-(tetrahydro-pyran-2-yloxy)-ethyl]-5*H*-1,2,4-triazino[5,6-*b*]indole

In a manner analogous to Example 64, using 3-(4-benzyl-3,5-dimethyl-pyrazol-1-yl)-5*H*-1,2,4-triazino[5,6-*b*]indole (Example 5, 70 mg, 200 µmol) and 2-(2-bromoethoxy)-tetrahydropyran (46 mg, 220 µmol), was prepared the title compound (90 mg, 93%). Hplc/ms (positive ion) Rt 4.85 min, m/z 483 ($M+H^+$).

Example 98: 3-(4-ethyl-3,5-dimethyl-pyrazol-1-yl)-5-[2-(tetrahydro-pyran-2-yloxy)-ethyl]-5*H*-1,2,4-triazino[5,6-*b*]indole

In a manner analogous to Example 64, using 3-(4-ethyl-3,5-dimethyl-pyrazol-1-yl)-5*H*-1,2,4-triazino[5,6-*b*]indole (Example 4, 58 mg, 200 µmol) and 2-(2-bromoethoxy)-tetrahydropyran (46 mg, 220 µmol), was prepared the title compound (60 mg, 71%). Hplc/ms (positive ion) Rt 4.53 min, m/z 421 ($M+H^+$).

Example 99: 2-[3-(4-benzyl-3,5-dimethyl-pyrazol-1-yl)-1,2,4-triazino[5,6-*b*]indol-5-yl]-ethanol

In a manner analogous to Example 85, using 3-(4-benzyl-3,5-dimethyl-pyrazol-1-yl)-5-[2-(tetrahydro-pyran-2-yloxy)-ethyl]-5*H*-1,2,4-triazino[5,6-*b*]indole (Example 97, 10 mg, 21 µmol), was prepared the title compound (5 mg, 60%). Hplc/ms (positive ion) Rt 4.09 min, m/z 399 ($M+H^+$).

Example 100: Activity Assay

The compounds of Examples 1, 3, 26, 28, 56, 73, 79, 80, 82, 84, 85, 87, 90 and 95 were tested for their inhibitory activity towards BACE.

All enzyme assays were performed at 20°C on an AlphaFusion (Packard Instruments) using 384 well plates (Greiner Bio-One Ltd). The assay volume was 30 µl. Inhibitors were dissolved in dimethyl sulphoxide (DMSO) and added into a well with 50 mM sodium acetate buffer pH 4.5 and 10 µM EDANS-EVNLDAEFK-DABCYL peptide substrate. The DMSO concentration was set at 10% in the assay.

The reaction was started with the addition of 1 µg/ml recombinant human soluble BACE-1. After 3 hours the fluorescence increase was measured in the plate reader at 365ex/485em. The EDANS-DABCYL peptide substrate becomes slightly fluorescent upon enzymatic cleavage due to disruption of the resonance energy transfer between the EDANS donor and DABCYL quenching acceptor in the intact substrate.

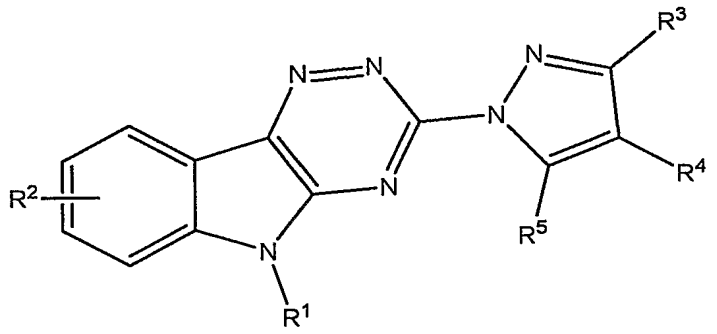
The activities (IC_{50} values in µM) of the tested Example compounds are tabulated below. The results demonstrate the desirability of compounds of the invention.

Compound	IC_{50}(µM)
1	38.3
3	5.7
26	4.2
28	9.1
56	3.7

73	3.1
79	9.7
80	2.5
82	5.3
84	5.9
85	28.8
87	12.0
90	9.4
95	5.8

CLAIMS

1. A compound for use in therapy, wherein the compound is of formula (I)



(I)

wherein

R^1 is hydrogen, alkyl, -alkyl-aryl, -alkyl-heterocycloalkyl or -alkyl-O-heterocycloalkyl;

R^2 is hydrogen, hydroxy, amino, nitro, alkoxy, alkyl, aryl or heteroaryl;

R^3 is hydrogen, alkyl or aryl;

R^4 is hydrogen, alkyl, aryl, heteroaryl, -CH(aryl)$_2$, -alkyl-aryl or -C(O)O-alkyl; and

R^5 is alkyl, hydroxy or amino;

or a pharmaceutically acceptable salt thereof.

2. A compound as defined in clam 1, independent of use, with the proviso that the compound is not a compound selected from:

2-(3,5-dimethyl-pyrazol-1-yl)-9-ethyl-9H-1,3,4,9-tetraaza-fluorene;

2-(3,5-dimethyl-pyrazol-1-yl)-9-methyl-9H-1,3,4,9-tetraaza-fluorene;

9-benzyl-2-(3,5-dimethyl-pyrazol-1-yl)-9H-1,3,4,9-tetraaza-fluorene;

9-benzyl-2-(4-benzyl-3,5-dimethyl-pyrazol-1-yl)-9H-1,3,4,9-tetraaza-fluorene;

4-benzyl-2-(9-benzyl-9H-1,3,4,9-tetraaza-fluoren-2-yl)-5-methyl-2H-pyrazol-3-ol;

2-(4-butyl-3,5-dimethyl-pyrazol-1-yl)-9-ethyl-9H-1,3,4,9-tetraaza-fluorene;

2-(4-benzyl-3,5-dimethyl-pyrazol-1-yl)-9-ethyl-9H-1,3,4,9-tetraaza-fluorene;

3-(3,5-dimethyl-pyrazol-1-yl)-5*H*-1,2,4-triazino[5,6-*b*]indole;

5-methyl-2-(5*H*-1,2,4-triazino[5,6-*b*]indol-3-yl)-2*H*-pyrazol-3-ol;

5-(4-chloro-phenyl)-2-(5*H*-1,2,4-triazino[5,6-*b*]indol-3-yl)-2*H*-pyrazol-3-ol;

3-(3,5-dimethyl-pyrazol-1-yl)-8-fluoro-5*H*-1,2,4-triazino[5,6-*b*]indole;

5-amino-1-(5-ethyl-5*H*-1,2,4-triazino[5,6-*b*]indol-3-yl)-1*H*-pyrazole-4-carboxylic acid ethyl ester;

5-amino-1-(5*H*-1,2,4-triazino[5,6-*b*]indol-3-yl)-1*H*-pyrazole-4-carboxylic acid ethyl ester;

5-phenyl-2-(5*H*-1,2,4-triazino[5,6-*b*]indol-3-yl)-2*H*-pyrazol-3-ylamine;

2-(5-methyl-5*H*-1,2,4-triazino[5,6-*b*]indol-3-yl)-5-phenyl-2*H*-pyrazol-3-ylamine;

5-(4-chloro-phenyl)-2-(5-methyl-5*H*-1,2,4-triazino[5,6-*b*]indol-3-yl)-2*H*-pyrazol-3-ylamine;

5-(4-bromo-phenyl)-2-(5-methyl-5*H*-1,2,4-triazino[5,6-*b*]indol-3-yl)-2*H*-pyrazol-3-ylamine;

5-(4-bromo-phenyl)-2-(5*H*-1,2,4-triazino[5,6-*b*]indol-3-yl)-2*H*-pyrazol-3-ylamine;

5-(4-chloro-phenyl)-2-(5*H*-1,2,4-triazino[5,6-*b*]indol-3-yl)-2*H*-pyrazol-3-ylamine;

2-(8-bromo-5*H*-1,2,4-triazino[5,6-*b*]indol-3-yl)-5-phenyl-2*H*-pyrazol-3-ylamine;

2-(8-bromo-5*H*-1,2,4-triazino[5,6-*b*]indol-3-yl)-5-(4-chloro-phenyl)-2*H*-pyrazol-3-ylamine; and

5-(4-bromo-phenyl)-2-(8-bromo-5*H*-1,2,4-triazino[5,6-*b*]indol-3-yl)-2*H*-pyrazol-3-ylamine.

3. A compound according to claim 1 or claim 2, wherein R^1 is hydrogen, methyl, ethyl, propyl, isopropyl, butyl, pyrazol-1-ylethyl, hydroxyethyl, (2-tetrahydro-pyran-2-yloxy)ethyl or benzyl.

4. A compound according to any preceding claim, wherein R^2 is hydrogen.

5. A compound according to any preceding claim, wherein R^3 is hydrogen, methyl or phenyl.

6. A compound according to any preceding claim, wherein R^4 is hydrogen,

methyl, ethyl, propyl, butyl or -C(O)O-CH_2CH_3.

7. A compound according to any of claims 1 to 5, wherein R^4 is phenyl, -CH(phenyl)$_2$, benzyl, 1-phenylethyl, 2-phenylethyl or napthylmethyl, any of which is optionally substituted.

8. A compound according to any of claims 1 to 5, wherein R^4 is quinolin-4-yl or pyridin-2-yl, either of which is optionally substituted.

9. A compound according to any preceding claim, wherein R^5 is hydrogen, methyl, hydroxy or amino.

10. A compound according to claim 1 or claim 2, selected from:

9-methyl-2-(5-methyl-3-phenyl-pyrazol-1-yl)-9H-1,3,4,9-tetraaza-fluorene;

2-(3,5-dimethyl-4-propyl-pyrazol-1-yl)-9-methyl-9H-1,3,4,9-tetraaza-fluorene; and

5-amino-1-(9-methyl-9H-1,3,4,9-tetraaza-fluoren-2-yl)-1H-pyrazole-4-carboxylic acid ethyl ester.

11. A compound according to claim 1 or claim 2, selected from:

3-(4-ethyl-3,5-dimethyl-pyrazol-1-yl)-5H-1,2,4-triazino[5,6-b]indole;

3-(4-benzyl-3,5-dimethyl-pyrazol-1-yl)-5H-1,2,4-triazino[5,6-b]indole;

3-[4-(2-benzyloxy-benzyl)-3,5-dimethyl-pyrazol-1-yl]-5H-1,2,4-triazino[5,6-b]indole;

4-[3,5-dimethyl-1-(5H-1,2,4-triazino[5,6-b]indol-3-yl)-1H-pyrazol-4-ylmethyl]-phenol;

2-[3,5-dimethyl-1-(5H-1,2,4-triazino[5,6-b]indol-3-yl)-1H-pyrazol-4-ylmethyl]-phenol;

3-[3,5-dimethyl-1-(5H-1,2,4-triazino[5,6-b]indol-3-yl)-1H-pyrazol-4-ylmethyl]-phenol;

3-[4-(3,5-dimethoxy-benzyl)-3,5-dimethyl-pyrazol-1-yl]-5H-1,2,4-triazino[5,6-b]indole;

3-(3,5-dimethyl-4-naphthalen-2-ylmethyl-pyrazol-1-yl)-5H-1,2,4-triazino[5,6-b]indole;

3-[4-(2-fluoro-benzyl)-3,5-dimethyl-pyrazol-1-yl]-5H-1,2,4-triazino[5,6-b]indole;

3-[3,5-dimethyl-4-(3-trifluoromethyl-benzyl)-pyrazol-1-yl]-5H-1,2,4-

triazino[5,6-b]indole;

3-[4-(2-methoxy-benzyl)-3,5-dimethyl-pyrazol-1-yl]-5-methyl-5H-1,2,4-triazino[5,6-b]indole;

3-[4-(3-fluoro-benzyl)-3,5-dimethyl-pyrazol-1-yl]-5-methyl-5H-1,2,4-triazino[5,6-b]indole;

3-[4-(3-methoxy-benzyl)-3,5-dimethyl-pyrazol-1-yl]-5-methyl-5H-1,2,4-triazino[5,6-b]indole;

3-[4-(3,5-dimethoxy-benzyl)-3,5-dimethyl-pyrazol-1-yl]-5-methyl-5H-1,2,4-triazino[5,6-b]indole;

3-[3,5-dimethyl-4-(2-nitro-benzyl)-pyrazol-1-yl]-5-methyl-5H-1,2,4-triazino[5,6-b]indole;

3-[4-(2-fluoro-benzyl)-3,5-dimethyl-pyrazol-1-yl]-5-methyl-5H-1,2,4-triazino[5,6-b]indole;

2-[3,5-dimethyl-1-(5-methyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)-1H-pyrazol-4-ylmethyl]-phenol;

3-[4-(4-methoxy-benzyl)-3,5-dimethyl-pyrazol-1-yl]-5-methyl-5H-1,2,4-triazino[5,6-b]indole;

3-[4-(2-benzyloxy-benzyl)-3,5-dimethyl-pyrazol-1-yl]-5-methyl-5H-1,2,4-triazino[5,6-b]indole;

3-(3,5-dimethyl-4-naphthalen-2-ylmethyl-pyrazol-1-yl)-5-methyl-5H-1,2,4-triazino[5,6-b]indole;

3-[3,5-dimethyl-4-(4-nitro-benzyl)-pyrazol-1-yl]-5-methyl-5H-1,2,4-triazino[5,6-b]indole;

4-[3,5-dimethyl-1-(5-methyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)-1H-pyrazol-4-ylmethyl]-phenol;

3-[3,5-dimethyl-1-(5-methyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)-1H-pyrazol-4-ylmethyl]-phenol;

3-[3,5-dimethyl-4-(4-trifluoromethyl-benzyl)-pyrazol-1-yl]-5-methyl-5H-1,2,4-triazino[5,6-b]indole;

3-[4-(4-methanesulphonyl-benzyl)-3,5-dimethyl-pyrazol-1-yl]-5-methyl-5H-1,2,4-triazino[5,6-b]indole;

3-[3,5-dimethyl-4-(2-trifluoromethyl-benzyl)-pyrazol-1-yl]-5-methyl-5H-

1,2,4-triazino[5,6-b]indole;

3-[3,5-dimethyl-4-(3-trifluoromethyl-benzyl)-pyrazol-1-yl]-5-methyl-5H-1,2,4-triazino[5,6-b]indole;

3-[3,5-dimethyl-4-(2-methyl-benzyl)-pyrazol-1-yl]-5-methyl-5H-1,2,4-triazino[5,6-b]indole;

3-[3,5-dimethyl-4-(3-methyl-benzyl)-pyrazol-1-yl]-5-methyl-5H-1,2,4-triazino[5,6-b]indole;

3-(3,5-dimethyl-4-phenethyl-pyrazol-1-yl)-5-methyl-5H-1,2,4-triazino[5,6-b]indole;

4-[3,5-dimethyl-1-(5-methyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)-1H-pyrazol-4-ylmethyl]-benzoic acid methyl ester;

3-[3,5-dimethyl-1-(5-methyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)-1H-pyrazol-4-ylmethyl]-benzoic acid methyl ester;

acetic acid 4-[3,5-dimethyl-1-(5-methyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)-1H-pyrazol-4-ylmethyl]-phenyl ester;

acetic acid 3-[3,5-dimethyl-1-(5-methyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)-1H-pyrazol-4-ylmethyl]-phenyl ester;

acetic acid 2-[3,5-dimethyl-1-(5-methyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)-1H-pyrazol-4-ylmethyl]-phenyl ester;

5-ethyl-3-[4-(2-methoxy-benzyl)-3,5-dimethyl-pyrazol-1-yl]-5H-1,2,4-triazino[5,6-b]indole;

5-ethyl-3-[4-(2-fluoro-benzyl)-3,5-dimethyl-pyrazol-1-yl]-5H-1,2,4-triazino[5,6-b]indole;

5-ethyl-3-[4-(3-fluoro-benzyl)-3,5-dimethyl-pyrazol-1-yl]-5H-1,2,4-triazino[5,6-b]indole;

5-ethyl-3-[4-(4-fluoro-benzyl)-3,5-dimethyl-pyrazol-1-yl]-5H-1,2,4-triazino[5,6-b]indole;

5-ethyl-3-[4-(3-methoxy-benzyl)-3,5-dimethyl-pyrazol-1-yl]-5H-1,2,4-triazino[5,6-b]indole;

3-[4-(3,5-dimethoxy-benzyl)-3,5-dimethyl-pyrazol-1-yl]-5-ethyl-5H-1,2,4-triazino[5,6-b]indole;

3-[3,5-dimethyl-4-(2-nitro-benzyl)-pyrazol-1-yl]-5-ethyl-5H-1,2,4-

triazino[5,6-b]indole;

2-[1-(5-ethyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)-3,5-dimethyl-1H-pyrazol-4-ylmethyl]-phenol;

5-ethyl-3-[4-(4-methoxy-benzyl)-3,5-dimethyl-pyrazol-1-yl]-5H-1,2,4-triazino[5,6-b]indole;

3-[4-(2-benzyloxy-benzyl)-3,5-dimethyl-pyrazol-1-yl]-5-ethyl-5H-1,2,4-triazino[5,6-b]indole;

3-(3,5-dimethyl-4-naphthalen-2-ylmethyl-pyrazol-1-yl)-5-ethyl-5H-1,2,4-triazino[5,6-b]indole;

3-[3,5-dimethyl-4-(3-nitro-benzyl)-pyrazol-1-yl]-5-ethyl-5H-1,2,4-triazino[5,6-b]indole;

3-[3,5-dimethyl-4-(4-nitro-benzyl)-pyrazol-1-yl]-5-ethyl-5H-1,2,4-triazino[5,6-b]indole;

4-[1-(5-ethyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)-3,5-dimethyl-1H-pyrazol-4-ylmethyl]-phenol;

3-[1-(5-ethyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)-3,5-dimethyl-1H-pyrazol-4-ylmethyl]-phenol;

3-[3,5-dimethyl-4-(4-trifluoromethyl-benzyl)-pyrazol-1-yl]-5-ethyl-5H-1,2,4-triazino[5,6-b]indole;

5-ethyl-3-[4-(4-methanesulphonyl-benzyl)-3,5-dimethyl-pyrazol-1-yl]-5H-1,2,4-triazino[5,6-b]indole;

3-[3,5-dimethyl-4-(2-trifluoromethyl-benzyl)-pyrazol-1-yl]-5-ethyl-5H-1,2,4-triazino[5,6-b]indole;

3-[3,5-dimethyl-4-(3-trifluoromethyl-benzyl)-pyrazol-1-yl]-5-ethyl-5H-1,2,4-triazino[5,6-b]indole;

3-[3,5-dimethyl-4-(2-methyl-benzyl)-pyrazol-1-yl]-5-ethyl-5H-1,2,4-triazino[5,6-b]indole;

3-[3,5-dimethyl-4-(3-methyl-benzyl)-pyrazol-1-yl]-5-ethyl-5H-1,2,4-triazino[5,6-b]indole;

3-(3,5-dimethyl-4-phenethyl-pyrazol-1-yl)-5-ethyl-5H-1,2,4-triazino[5,6-b]indole;

4-[1-(5-ethyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)-3,5-dimethyl-1H-pyrazol-4-

ylmethyl]-benzoic acid methyl ester;

3-[1-(5-ethyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)-3,5-dimethyl-1H-pyrazol-4-ylmethyl]-benzoic acid methyl ester;

4-[1-(5-ethyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)-3,5-dimethyl-1H-pyrazol-4-ylmethyl]-benzoic acid;

3-(3,5-dimethyl-4-propyl-pyrazol-1-yl)-5-ethyl-5H-1,2,4-triazino[5,6-b]indole;

5-ethyl-3-(4-ethyl-3,5-dimethyl-pyrazol-1-yl)-5H-1,2,4-triazino[5,6-b]indole;

3-(4-benzyl-3,5-dimethyl-pyrazol-1-yl)-5-propyl-5H-1,2,4-triazino[5,6-b]indole;

5-propyl-3-(3,4,5-trimethyl-pyrazol-1-yl)-5H-1,2,4-triazino[5,6-b]indole;

3-(4-ethyl-3,5-dimethyl-pyrazol-1-yl)-5-propyl-5H-1,2,4-triazino[5,6-b]indole;

3-(3,5-dimethyl-4-propyl-pyrazol-1-yl)-5-propyl-5H-1,2,4-triazino[5,6-b]indole;

5-butyl-3-(3,5-dimethyl-pyrazol-1-yl)-5H-1,2,4-triazino[5,6-b]indole;

5-butyl-3-(3,4,5-trimethyl-pyrazol-1-yl)-5H-1,2,4-triazino[5,6-b]indole;

3-(4-benzyl-3,5-dimethyl-pyrazol-1-yl)-5-butyl-5H-1,2,4-triazino[5,6-b]indole;

5-butyl-3-(3,5-dimethyl-4-naphthalen-2-ylmethyl-pyrazol-1-yl)-5H-1,2,4-triazino[5,6-b]indole;

5-butyl-3-[4-(2-fluoro-benzyl)-3,5-dimethyl-pyrazol-1-yl]-5H-1,2,4-triazino[5,6-b]indole;

5-butyl-3-[3,5-dimethyl-4-(3-trifluoromethyl-benzyl)-pyrazol-1-yl]-5H-1,2,4-triazino[5,6-b]indole;

5-butyl-3-(4-ethyl-3,5-dimethyl-pyrazol-1-yl)-5H-1,2,4-triazino[5,6-b]indole;

5-benzyl-3-(3,4,5-trimethyl-pyrazol-1-yl)-5H-1,2,4-triazino[5,6-b]indole;

3-(4-benzyl-3,5-dimethyl-pyrazol-1-yl)-5-isobutyl-5H-1,2,4-triazino[5,6-b]indole;

5-benzyl-3-(3,5-dimethyl-4-propyl-pyrazol-1-yl)-5H-1,2,4-triazino[5,6-b]indole;

oxalic acid 4-[3,5-dimethyl-1-(5-methyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)-

1H-pyrazol-4-ylmethyl]-phenyl ester ethyl ester;

5-isobutyl-3-(3,4,5-trimethyl-pyrazol-1-yl)-5H-1,2,4-triazino[5,6-b]indole;

3-(4-ethyl-3,5-dimethyl-pyrazol-1-yl)-5-isobutyl-5H-1,2,4-triazino[5,6-b]indole;

3-(3,5-dimethyl-4-propyl-pyrazol-1-yl)-5-isobutyl-5H-1,2,4-triazino[5,6-b]indole;

3-(3,5-dimethyl-4-propyl-pyrazol-1-yl)-5-(2-pyrrolidin-1-yl-ethyl)-5H-1,2,4-triazino[5,6-b]indole;

2-[3-(3,5-dimethyl-4-propyl-pyrazol-1-yl)-1,2,4-triazino[5,6-b]indol-5-yl]-ethanol;

3-[3,5-dimethyl-4-(1-phenyl-ethyl)-pyrazol-1-yl]-5-methyl-5H-1,2,4-triazino[5,6-b]indole;

3-(4-benzhydryl-3,5-dimethyl-pyrazol-1-yl)-5-methyl-5H-1,2,4-triazino[5,6-b]indole;

3-[3,5-dimethyl-4-(1-phenyl-ethyl)-pyrazol-1-yl]-5-ethyl-5H-1,2,4-triazino[5,6-b]indole;

3-(4-benzhydryl-3,5-dimethyl-pyrazol-1-yl)-5-ethyl-5H-1,2,4-triazino[5,6-b]indole;

3-[4-(4-methoxy-phenyl)-pyrazol-1-yl]-5-methyl-5H-1,2,4-triazino[5,6-b]indole;

3-[4-(3-bromo-phenyl)-pyrazol-1-yl]-5-methyl-5H-1,2,4-triazino[5,6-b]indole;

5-methyl-3-(4-quinolin-4-yl-pyrazol-1-yl)-5H-1,2,4-triazino[5,6-b]indole;

5-methyl-3-(4-pyridin-2-yl-pyrazol-1-yl)-5H-1,2,4-triazino[5,6-b]indole;

3-[4-(4-bromo-phenyl)-pyrazol-1-yl]-5-methyl-5H-1,2,4-triazino[5,6-b]indole;

3-(3,5-dimethyl-4-propyl-pyrazol-1-yl)-5-[2-(tetrahydro-pyran-2-yloxy)-ethyl]-5H-1,2,4-triazino[5,6-b]indole;

5-[2-(tetrahydro-pyran-2-yloxy)-ethyl]-3-(3,4,5-trimethyl-pyrazol-1-yl)-5H-1,2,4-triazino[5,6-b]indole;

3-(4-benzyl-3,5-dimethyl-pyrazol-1-yl)-5-[2-(tetrahydro-pyran-2-yloxy)-ethyl]-5H-1,2,4-triazino[5,6-b]indole;

3-(4-ethyl-3,5-dimethyl-pyrazol-1-yl)-5-[2-(tetrahydro-pyran-2-yloxy)-ethyl]-5H-1,2,4-triazino[5,6-b]indole; and

2-[3-(4-benzyl-3,5-dimethyl-pyrazol-1-yl)-1,2,4-triazino[5,6-b]indol-5-yl]-ethanol.

12. A pharmaceutical composition comprising a compound according to any preceding claim, together with a pharmaceutically acceptable carrier or diluent.

13. Use of a compound of any of claims 1 to 11, for the manufacture of a medicament for the treatment or prevention of Alzheimer's disease.

INTERNATIONAL SEARCH REPORT

ational Application No
.../GB2004/001761

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D487/04 A61P25/28 A61K31/53

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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A	US 2003/078166 A1 (KNEGTEL RONALD ET AL) 24 April 2003 (2003-04-24) claim 1 -----	1-13
A	ESHBA N H ET AL: "Synthesis of some substituted 1,2,4-triazino'5,6-b!indole derivatives as potential antiviral and anticancer agents" PHARMAZIE, VEB VERLAG VOLK UND GESUNDHEIT. BERLIN, DD, vol. 42, no. 10, 1987, pages 664-666, XP009029588 ISSN: 0031-7144 p. 664, compounds 28-36 ----- -/--	1-13

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 September 2004	20/09/2004

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1

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB2004/001761

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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